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Editorial

Roberto Ferrari, MD, PhD
David J. Hearse, BSc, PhD

CARDIO-ONCOLOGY:
TO HYPHENATE OR NOT TO HYPHENATE?

Readers of Dialogues in Cardiovascular Medicine may wonder why a cardiologist should be receiving an issue devoted to cardio-oncology. To date, there are a mere 25 citations of this word in titles of articles in PubMed. In 1996—coincidentally the very same year the first issue of Dialogues went to print—Daniela Cardinale published so to speak the maiden article on the topic, announcing “A new frontier: cardio-oncology.” Twelve years elapsed before the second citation in a title, in 2008. The latest addition to the list dates back to May 2013, with Javid Moslehi and Susan Cheng referring in their paper to cardio-oncology as an “emerging discipline,” as does Bernard Lévy in the Lead Article of this issue of Dialogues.

An emerging discipline is by necessity a hot topic, so there are some very good reasons for publishing an issue of Dialogues on cardio-oncology today. These two “hyphenated” disciplines—cardiology and oncology—have a lot in common in terms of research, and even though oncologists have been enjoying quite a head start, cardiologists are now catching up. To take a topic like “apoptosis,” cardiologists have been showing increasing interest in the mechanisms of apoptosis and how it is triggered, whether in relation to the endothelium or to the myocyte, as they have been realizing that an excess of apoptosis is linked to the onset and progression of atherosclerosis as well as to postischemic remodeling, ultimately leading to heart failure. Beyond apoptosis, there is also growing interest in the regeneration of endothelial cells, leading to neovascularization, and the prospects of complete repair with major strides being made in the understanding of regeneration of the myocyte.

If we now turn to practical, in other words, clinical, applications, our two “hyphenated” disciplines tug and pull and want to “dehyphenate,” assuming mirror images of each other. What does the cardiologist want? The cardiologist must fight against apoptosis and favor regeneration. And what does the oncologist want? The exact opposite of the oncologist, by seeking to improve apoptosis and suppress regeneration, so as to forestall neoangiogenesis. Different angles indeed.
So what are you going to read about in *Dialogues*? **Bernard Lévy**, who leads this issue, expounds on the substantial risk of developing heart disease as a result of chemotherapy and/or radiation therapy. **Paola Rizzo** and **Donato Mele** explore a fascinating pathway, the so called Notch pathway, which decides the fate of the cell. Modulation of this pathway could be a promising therapeutic area for both cardiology and oncology. **Thor Edvardsen** and **Sebastian Sarvari** praise our colleagues the oncologists for now having extremely powerful chemotherapy protocols to fight cancer, but point out that these come with a risk of cardiotoxicity, since the drugs used act on several pathways such as the ERG system, GPL30, and possibly the Notch pathway. It is therefore mandatory for the cardiologist to recognize and counter cardiac toxicity as early as possible in order to be able to continue the chemotherapy and achieve full efficacy. The authors discuss the best tools for early diagnosis and suggest setting up guidelines. Finally, **Michel Safar** examines the interactions between macro- and microcirculation and explores their interactions in patients with cardiovascular disease and cancer.

Much still lies ahead in the “hyphenated” field of cardio-oncology, and we hope that this issue of *Dialogues* will make this topic less of a terra incognita by mapping out some of the most promising avenues of research and clinical applications.
Cardio- oncology: an emerging discipline

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Cardiac disease in patients receiving cancer care has been hitherto rarely discussed as an aspect of cardiology. However, over the last 20 years, the survival rate of cancer patients has increased in relation with the progress of oncological treatments, while, logically, the incidence of side effects associated with intensive, more complex, and longer antitumor treatments has increased in parallel. Cardiotoxicity is a common complication associated with many antitumor agents and may compromise the clinical course and patient survival and quality of life, independently of cancer prognosis. Likewise, the development of new biologic and targeted cancer therapies has resulted in increased cancer survival, but has introduced new and sometimes unexpected cardiovascular side effects. The impressive recent and still ongoing development of new antiangiogenic agents, often used in bitherapy or tritherapy, is associated with new and specific cardiovascular adverse effects, generally arterial hypertension, and possibly leading to heart failure. Cardio-oncology is an emerging discipline that addresses cardiovascular toxicity in preclinical, clinical, and therapeutic aspects of protocol development, treatment, and surveillance of patients being treated for cancer.

A bout 12 million people in the USA are diagnosed with cancer, with breast cancer and prostate cancer each accounting for more than 2 million cases. 1 Approximately 66% are expected to live at least 5 years after diagnosis. 2 Yet cardiac death remains more prevalent than cancer in people older than 65 years in the whole population, and cardiovascular disease (CVD) accounts for half of non–cancer-related mortality after diagnosis of cancer (Figure 1, page 6). The highest-risk populations are men receiving hormone therapy for prostate cancer and patients receiving anthracyclines and chest radiation. 3 A study of more than 2000 testicular cancer survivors showed, for example, a twofold increase in the risk of myocardial infarction in survivors younger than 45 years compared with the age-matched general population. 4 Likewise, the 10-year risk of a serious cardiovascular event was as high as breast cancer recurrence in almost 80% of patients in a postmenopausal cohort of patients with breast cancer. 5

CARDIAC RESPONSES TO INJURY

Response to cell loss

Despite the recently evidenced presence of resident myocardial stem cells, the heart recovers only poorly from cell loss, and cardiac myocytes are not capable of extensive cell replacement after cardiotoxic treatments. Myocardial tissue lacks the enzyme catalase and thus has only limited capacity to reduce the oxidative stress caused by anthracyclines and other drugs used in cancer therapy. Abnormal oxidative stress changes the equilibrium between protein degradation and synthesis and, when pronounced, also activates caspases, which induce cardiomyocyte apoptosis or necrosis. 6 Exposure to toxic substances such as anticancer drugs, but also alcohol and cocaine, is known to cause cardiac damage and alter heart response to myocyte loss. 7

In contrast, the heart is far more able to address reduction in its healthy muscle mass via physiological adaptation mechanisms such as the Frank-Starling mechanism and/or various mechanisms grouped un-
nder the term “remodeling,” ie, basically, myocardial hypertrophy, fibrosis, and ventricular wall thickening. Thus, the heart has the capacity to increase cardiac output through exercise and the ability to survive the loss of a large number of myocytes through a variety of insults, such as myocardial infarction and toxic agents.

**Response to cardiac dysfunction**

Much of the literature on the cardiotoxicity of cancer treatment focuses on cardiomyopathy, but this condition is only one of several abnormalities that can impair cardiovascular function. Effects on the blood vessels can result in ischemia or changes in blood pressure and, in the pericardium, anticancer therapy might cause an imbalance in fluid equilibrium or pericardial fibrosis, thickening, and stiffening. Further- more, anticancer therapy might increase the risk of arrhythmias in patients predisposed to cardiac ectopy. Several of these processes can be exacerbated directly by the tumor, which might result in local inflammation near the heart or serve as an arrhythmogenic focus.

**The difficulty of recognizing early cardiac damage**

The remarkable capacity of the heart to compensate for myocyte loss or dysfunction results in the difficulty to diagnose cardiac injury based on functional parameters: the potential for cardiac adaptation is largely exhausted when clinically relevant cardiac dysfunction is observed. From that point onward, clinical deterioration accelerates and deterioration may be very rapid. Since decreased left ventricular ejection fraction (LVEF) ensues only after full compensation is no longer achieved, maintained left ventricular (LV) function as measured by cardiac ultrasound or nuclear techniques should be considered neither as an indicator of normal myocardium nor as an evidence of an absence of cardiotoxicity. Early damage may not be recognized by these parameters, and biomarkers, which are not yet part of routine clinical setting, may have considerable potential.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
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<td>CPG</td>
<td>clinical practice guidelines</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<td>EGFR</td>
<td>epidermal growth factor receptor</td>
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<td>HER</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-B-type natriuretic peptide</td>
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<tr>
<td>VEGF(R)</td>
<td>vascular endothelial growth factor (receptor)</td>
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CAR DI AC DYSFUNCTION  
AND CANCER TREATMENTS

Radiation-induced heart disease

External radiation of the thorax can induce cardiac adverse effects such as acute and chronic pericarditis, pericardial effusion, accelerated coronary artery disease, restrictive cardiomyopathy, valve abnormalities, conduction system abnormalities, and, rarely, secondary cardiac tumors. The development of radiation-related cardiac disease depends on the radiation dose, the volume of heart exposed, and the radiation delivery technique used. The malignancies most commonly treated by means of chest radiation therapy and, therefore, associated with cardiac disease, include lymphoma, breast cancer, and lung cancer. The concurrent use of radiation therapy and chemotherapy may have additive cardiotoxic effects.

The patient’s age at the time of exposure is important to consider: young patients (<20 years) are at higher risk than their older counterparts, possibly because they are still developing and have a higher rate of cellular turnover, and are thus more susceptible to DNA damage. 

10 The lower dose threshold for radiation associated with heart disease is around 15 Gy, with disease frequently increasing at doses above 40 Gy. Incidence of cardiac complications also increases when more than 50% of the volume of the heart is contained in the radiation field. The mechanism of cardiac damage from radiation is thought to consist of microvascular destruction and apoptosis from direct cellular injury. 

11 Fibrosis is the ultimate outcome, occurring years later. The exact incidence of radiation-related heart disease is difficult to estimate because of the long delay between radiation exposure and development of disease. Radiation therapy may also cause fibrous thickening of the pericardium, which may lead to pericarditis, pericardial effusion, and, rarely, cardiac tamponade. The right side of the heart is more frequently involved. There is a high prevalence of diastolic dysfunction in asymptomatic patients after mediastinal irradiation, most likely due to myocardial fibrosis. The presence of diastolic dysfunction is associated with stress-induced ischemia and worse prognosis. 

12 Treatment of the left breast for cancer is associated with a higher risk of cardiac complications than is right-sided disease, presumably owing to increased cardiac exposure to radiation. 

In the Childhood Cancer Survivor Study, an increased risk of heart failure, myocardial infarction, pericardial disease, and valve disease was reported among more than 14,000 patients. Hazard ratios for these events ranged from 2.2 to 5.5 at total radiation doses to the heart from 15 to more than 35 Gy. The incidence of heart disease continued to increase, even 30 years following exposure. Another study of 4122 patients found even more striking results: the relative risk of cardiac death was 12.5 at radiation doses of 5 to 15 Gy and 25.1 at doses greater than 15 Gy. 

15 The most common lesions after chest irradiation are tricuspid regurgitation, mitral regurgitation, and aortic regurgitation; aortic stenosis is also occasionally encountered. Histologically, the valves show endocardium fibrosis and thickening. 

16 Changes to valves on the left side are more common than those on the right side. A significantly higher risk of death due to ischemic heart disease has been reported in patients receiving radiotherapy for Hodgkin’s disease and breast cancer, although a fair number of patients remain asymptomatic. 

17 Coronary artery disease after radiation therapy is mainly related to endovascular proliferation and accelerated atherosclerosis. 

18 Because of its location, the left anterior descending artery is the vessel most frequently affected by radiation therapy. 

19 Macrovacular coronary alterations can result in angina, myocardial infarction, or sudden cardiac arrest, and risk increases with time. Traditional cardiac risk factors, such as dyslipidemia, have a key role in promoting the pathogenesis of radiation-related coronary artery disease.

Restrictive cardiomyopathy can be very difficult to distinguish from pericardial constrictions, especially since both can be present in the same patient. Valve disease is common, but is usually not severe; nevertheless, it contributes to the high morbidity associated with the irradiated heart. 

Two recent comparable studies reported an increased risk of heart failure and valve dysfunction in irradiated breast cancer patients as well as higher rates of myocardial infarction and coronary artery disease associated with radiation of the left hemithorax. However, improvements in radiation techniques, such as electron beam radiation, conformal radiation therapy, improved cardiac shielding, and respiratory gating, have led to a considerable reduction in cardiac radiation exposure and thus reduction in risk of cardiac adverse effects.

Agents with direct cardiotoxic effects

Anthracycline antibiotics are among the most effective anticancer agents introduced over the past 50 years, and are still widely used in the treatment of breast can-
cer, lymphoma, leukemia, and sarcomas. Their use has been limited by their cardiotoxicity. Anthracycline cardiotoxicity is a form of irreversible nonischemic toxic cardiomyopathy. Cardiac damage may be subclinical and, thus, diagnosed only after compensatory mechanisms are exhausted, which explains why cardiotoxicity may not manifest for years, or in some instances decades, after anthracycline treatment. Acute manifestations occurring during chemotherapy include troponin elevation, electrocardiogram changes, dysrhythmia, and, occasionally, pericarditis. Biopsy specimens in this period confirm early myocyte damage despite preserved LVEF. 23

Typically, anthracycline-related cardiotoxicity presents as LV dysfunction months or years after exposure. As with other forms of progressive heart failure (HF), it is assumed that considerable remodeling and compensatory mechanisms are involved. When severe, even late anthracycline cardiotoxicity may progress to advanced HF and end-stage heart disease.

Anthracycline cardiotoxicity is related to the cumulative dose administered. Initially, it was estimated that a cumulative dose of approximately 500 mg/m² of doxorubicin correlated with a 5% likelihood of developing HF. 24 More recent retrospective analyses suggest that doxorubicin cardiotoxicity occurs at cumulative doses considerably lower than first appreciated and that a 5% incidence of HF occurs with a cumulative dose of 400 to 450 mg/m². 25

Since the 1980s, there has been a marked decrease in cumulative anthracycline exposure with a concurrent reduction in incidence of associated cardiotoxicity. Nevertheless, some myocyte damage occurs even at low doses and renders patients more susceptible to the development of HF when sequential stresses are encountered. 26 Recent evidence in more than 40,000 women with breast cancer suggests a significant problem, at least in the more elderly patients. 27 Other significant baseline predictors of increased risk were peripheral and coronary artery disease, diabetes, and hypertension.

Doxorubicin and epirubicin are the most used anthracyclines. Epirubicin is widely used in the treatment of breast cancer, but also in the treatment of a number of other solid tumors. 28 In experimental models, cardiac toxicity of epirubicin is similar to that of doxorubicin. 29 In patients, the cardiotoxicity of epirubicin is generally thought to be less than that of the parent compound when given in doses that result in equivalent myelo-suppression, ie, approximately one-third of the parent compound dose. This reduced cardiotoxicity of epirubicin was confirmed by a meta-analysis of clinical studies comparing epirubicin and doxorubicin, which showed a strong trend toward fewer cardiac events with epirubicin. 30

Various formulations have been used to try to limit the cardiotoxicity of anthracyclines. Liposomal formulations offer substantial cardioprotection, in part by increasing the size of anthracycline molecules through encapsulation. These larger molecules are thought to remain intravascular in normal vascular beds, such as the heart, but penetrate more readily into tumors, which have an immature vascular system. 31 Pegylated liposomal doxorubicin, the most widely used formulation, is approved for use in the treatment of ovarian cancer, multiple myeloma, and acquired immunodeficiency syndrome (AIDS)-related Kaposi’s sarcoma. It is also used in the treatment of metastatic breast cancer and lymphoma.

**Targeted cancer therapy may also affect cardiac function**

Human epidermal growth factor receptors (HER) are proteins embedded in the cell membrane that trigger molecular signals from outside to inside the cell and switch genes on and off. HER proteins regulate cell growth, survival, adhesion, migration, and differentiation functions, which are amplified or weakened in cancer cells. In some cancers, notably some forms of breast cancer, HER2 is overexpressed and causes breast cells to multiply uncontrollably. Activation of HER2 signaling pathways in cardiomyocytes appears to improve cell adaptation to increased mechanical stress and promote cell survival. 32 Mice with ventricle-restricted deletion of the HER2 gene demonstrate spontaneous LV failure, respond poorly to stress, and their myocytes are particularly susceptible to anthracycline toxicity. 33

**Trastuzumab** is a monoclonal antibody that interferes with the HER2 receptor and is mainly used to treat certain forms of breast cancer. It reduces the risk of recurrence at 3 years nearly by half and improves survival by about one-third. However, major trials have consistently shown an increased relative risk of New York Heart Association (NYHA) class III–IV heart failure with an incidence ranging from 0% to 3.9%. 34 The risk of cardiac dysfunction increases in the following situations: (i) at lower levels of baseline LVEF; (ii) with higher cumulative doses of anthracyclines given before trastuzumab; (iii) with advanced age; (iv) with current

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or previous use of antihypertensive agents, and (v) with higher body mass indexes. Cardiotoxicity is relatively rare with trastuzumab used in monotherapy. In contrast to anthracyclines, with which cardiac toxicity frequently becomes clinically significant months to years after the initial treatment, trastuzumab-associated cardiotoxicity predominantly occurs during the course of trastuzumab treatment. Cardiac function generally recovers within 6 months following termination of therapy with trastuzumab. Reexposure to trastuzumab after recovery from LV dysfunction is generally well tolerated. Based on growing evidence, a distinction can be made between Type I and Type II cardiotoxicity, whereby Type I reflects the scenario of damage associated with myocyte death and Type II is more benign and is associated with cell hibernation or myocardial stunning.

- **Lapatinib** is a dual tyrosine kinase inhibitor that blocks both epidermal growth factor receptor (EGFR) and HER2 kinases; it is an orally active drug used in the treatment of breast cancer and other solid tumors. In a prospective study evaluating LVEF in 3,689 patients who received lapatinib (alone or in combination) in the course of 44 phase 1–3 studies, no cardiac deaths were attributed to lapatinib, and significant HF occurred in only 0.2% of patients while 1.4% had an asymptomatic decline in LVEF of more than 20%. However, lack of standardization of cardiotoxicity criteria makes comparison of outcomes across studies difficult. Notwithstanding these concerns, of those patients with cardiac events, 88% recovered to some degree, suggesting that lapatinib is an agent exhibiting the Type II (nonpermanent) form of cardiac impairment. Data from patients who received lapatinib for more than 6 months do not suggest cumulative dose-related cardiotoxicity.

- In another study, patients with advanced HER2-positive breast cancer and normal LVEF were randomly assigned to receive lapatinib plus capecitabine or capecitabine alone. All had been previously exposed to an anthracycline, a taxane, and trastuzumab. No symptomatic decrease in LVEF was reported in either group.

- 5-Fluorouracil and the prodrug capecitabine are associated with myocardial ischemia and, rarely, infarction. These agents probably induce ischemia through coronary artery spasm; ischemia is more frequently encountered in patients with preexisting coronary artery disease.

- Paclitaxel and docetaxel are also associated with cardiac ischemia, but ischemia is rare with these agents.

- Arsenic trioxide antiemetics and antimicrobials have been associated with QT prolongation, and these agents should be used with caution, and patients monitored.

### Antiangiogenic drugs, direct and indirect effects on heart function

Proliferation of new blood vessels is necessary for tumors to grow and contributes to the spread of metastases. The idea that blocking angiogenesis could be used as a therapeutic strategy in cancer biology was initially proposed in 1971 by Judah Folkman. Since then, targeting angiogenesis has become an appealing therapeutic approach with broad applications. The first clinically available antiangiogenic drug was bevacizumab, a monoclonal antibody targeted against soluble vascular endothelial growth factor (VEGF) protein. It was approved by the Food and Drug Administration in 2004 for the treatment of metastatic colorectal cancer, bevacizumab is now licensed to treat various cancers, including colorectal, lung, breast (outside the USA), glioblastoma (USA only), kidney, and ovarian. Small receptor tyrosine kinase inhibitors, with potent VEGFR-2 inhibition, have also been approved for a range of malignancies. Receptor tyrosine kinase inhibitors are not entirely specific for VEGFR-2 and target other tyrosine kinase receptors. For example, sunitinib and sorafenib, the first receptor tyrosine kinase inhibitors with potent anti-VEGFR inhibition, also target platelet-derived growth factor receptor, as well as c-kit (receptor for stem cell factor). The multiple receptor tyrosine kinase targets of these drugs explains both their therapeutic potency and their cardiotoxicity. The antiangiogenic agents bevacizumab, sunitinib, and sorafenib are also associated with significant systemic hypertension in as many as one-third of patients and are considered partly responsible for the modest risk of LV dysfunction. Serious complications such as stroke are rare, but have been reported.

Cardiovascular monitoring is crucial given the evidence that hypertension, arterial thromboembolism, and HF are among the potentially serious toxic effects of bevacizumab. Hypertension with secondary LV dysfunction, rather than primary myocardial toxicity, may play a part in the decrease in LVEF. Initial clinical trials with bevacizumab identified hypertension in 28% of patients and subsequent trials with sorafenib, sunitinib, and pazopanib identified hypertension with similar frequency in all three. Meta-analyses have shown the incidence of hypertension to be from 19% to 24% in all classes of angiogenesis inhibitors. Interestingly, the rise in blood pressure associated with VEGF inhibitors...
appears to reverse as rapidly as it sets in, with a return of blood pressure to near-baseline levels by the end of the off-treatment phase, an observation that has useful implications for patient management. A phase 2 trial on the feasibility of adding bevacizumab to an adjuvant regimen of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel suggests that 10% of patients experienced a >10% decrease in LVEF after eight cycles. Symptomatic cardiotoxicity was reported in 18% of renal cancer patients treated with sunitinib or sorafenib. Cancers and hypertension preferentially occur in the same older population; thus they are often comorbid conditions. Underlying hypertension and/or antihypertensive therapy increases the risk of chemotherapy-related LV systolic dysfunction. It should be noted, however that hypertension with secondary LV dysfunction may be involved, rather than primary myocardial toxicity.

A number of pathophysiological mechanisms have been proposed to explain antiangiogenic-associated hypertension. Activation of VEGFR-2 by VEGF induces expression of nitric oxide (NO) in endothelial cells, which promotes vascular permeability and vasodilation. Logically, treatments that target VEGF and VEGF receptors have been shown to decrease NO synthesis and lead to hypertension, suggesting an important causal role for impaired NO production in the pathogenesis of antiangiogenic-mediated hypertension. Other mechanisms are likely involved. Loss of parallel capillary circulation in normal, nontumor tissue (ie, capillary rarefaction) has also been associated with hypertension in patients treated with angiogenesis inhibitors. Endothelial dysfunction, leading to an increase in endothelin-1 and aortic stiffness, has also been evoked in the pathophysiology of antiangiogenic-related hypertension.

**Antiangiogenic agents and heart failure**

Besides hypertension, another fascinating mechanism may be involved in the genesis of HF. In experimental models, administration of a VEGF trap reagent able to block signaling of all VEGF isoforms to mice subjected to pressure overload by surgical aortic constriction resulted in diminished cardiac hypertrophy and promoted the progression to heart failure. In conditional transgenic mice, sequential development of adaptive cardiac hypertrophy with preserved contractility in the acute phase followed by dilated cardiomyopathy in the chronic phase was observed after the induction of activated Akt1 gene in the heart. In this setting, coronary angiogenesis was enhanced during the phase of adaptive cardiac growth, but decreased as hearts underwent pathological remodeling. These results strongly suggest that inactivation of endogenous VEGF impaired adaptive cardiac hypertrophy in response to pressure overload and contributed to the rapid progression from compensatory cardiac hypertrophy to heart failure. This underlines the importance of microvascular plasticity to allow adaptation of the vascular network and, thus, of oxygen supply, to the increased metabolic demand related to pressure overload. Adapted microvascular plasticity allows compensatory cardiac hypertrophy. In the absence of such vascular plasticity due to VEGF blockade, myocardium hypertrophy is unable to develop, thereby contributing to the development of cardiac failure, ie, to cardiomyocytes in vivo ultimately becoming maladaptive.

**DIAGNOSIS OF CARDIOTOXICITY**

**Current approaches: assessment of LVEF by echography and/or multigated acquisition scanning**

The most frequent clinical manifestation of cardiotoxicity is asymptomatic left ventricular dysfunction. In clinical oncology practice, regular cardiac function assessment is recommended by guidelines to detect early cardiotoxicity through evaluation of left ventricular ejection function by either echocardiography or multigated acquisition scanning. However, some major limitations of this approach must be highlighted. First, monitoring of all patients treated with chemotherapy as frequently as suggested by the guidelines impacts the overall cost of care, as well as exposing the patient to unnecessary radiation if scanning is used. Moreover, as pointed out above, the utility of monitoring cardiac function by evaluating LVEF only is questionable and this parameter seems to be neither sensitive nor specific enough to predict late declines in cardiac function. Indeed, cardiac damage is usually detected only when functional impairment has already occurred, which means that early preventive strategy is impossible. When cardiac dysfunction evidenced by a decrease in LVEF develops, complete cardiac recovery occurs in only 42% of patients, despite optimal pharmacological therapy. On the other hand, evidence of unaltered heart function during chemotherapy does not preclude late cardiac deterioration.

Thus, there is a need for sensitive and cardiospecific biomarkers allowing early identification, assessment, and monitoring of cardiotoxicity. This approach is minimally invasive, less expensive, and can easily be re-
peated. Moreover, interpretation of the results is less dependent on the expertise of the operator, thus avoiding the possibility of observer variability. 64

**Biomarkers in the management of cardiotoxic cancer drugs**

**Cardiac troponins**

Since 2000, cardiac troponins have been defined as the biomarkers of choice for assessing acute myocardial damage. 65 Troponin elevation correlates with clinical severity and with life expectancy in patients with acute coronary syndromes. Troponin evaluation is thus used not only for identification of myocardial injury, but also for cardiac risk stratification in different situations of cardiac injury such as left ventricular hypertrophy, congestive heart failure, pulmonary embolism, blunt trauma, sepsis, and diabetes mellitus. 66 Low cost, wide availability, and extensive validation in other forms of heart disease make troponin attractive as a potentially sensitive tool for the detection of early chemotherapy damage. Troponin is a sensitive and specific marker for myocardial injury in patients treated with anticancer drugs and is able to predict, at a very early stage, both the development of future left ventricular dysfunction and its severity. 67-69 Troponin is also able to detect cardiac events at a later stage in a large population with a long follow-up. Three different degrees of cardiac risk have been identified, according to three distinct troponin I patterns. Patients without troponin I elevation after chemotherapy showed no significant reduction in LVEF (Figure 2) 64 and had a good prognosis, with a 1% incidence of cardiac events during the more than 3-year-long follow-up. Hence, in consideration of the high negative predictive value of troponin (99%), low-risk patients, in whom no close cardiac surveillance after chemotherapy is required, may accurately be identified. In contrast, troponin I-positive patients had a greater incidence of major adverse cardiac events. Furthermore, among troponin I-positive patients, persistence of elevation 1 month after chemotherapy was consistent with a higher incidence of events than in patients showing only a transient increase (84% versus 37%, \( P<0.001 \)). 70 Troponin T increase was reported in 15% of patients treated with anthracycline chemotherapy 71,72 In these patients, a significantly greater drop in LVEF was observed during the following 12 months than in patients with no increase in troponin. Finally, in the first 3 to 5 days after administration of a standard dose of chemotherapy, an increased troponin T level was observed in 34% of patients, which was predictive of left ventricular diastolic dysfunction. In the same way, trastuzumab-induced cardiotoxicity is significantly more frequent in patients showing an increase in troponin I during treatment than in those without troponin I increase (62% versus 5%, \( P<0.001 \)). 64 In addition, the relative risk for no recovery from cardiac dysfunction in response to heart failure therapy is about 3-fold greater in troponin I-positive patients than in troponin I-negative patients (relative risk, 2.9; confidence interval [CI] 95%, 1.7-3.9, \( P<0.001 \)).

These data suggest that troponin I should be obtained in all patients undergoing chemotherapy to assess cardiac risk of both previous and new antineoplastic treatments, regardless of the mechanism underlying their cardiac toxic effect. Its measurement should also be included among the criteria used to define cardiotoxicity early in the preclinical development of new antitumoral drugs. It is necessary to collect blood samples at several time periods to document a potential increase in plasma concentration of troponin. 73,74 However, the time point at which a negative troponin value reaches 100% of specificity for no further troponin release still cannot be defined; this represents a possible limitation for using this marker in clinical practice.
Natriuretic peptides

Natriuretic peptides are commonly used as sensitive markers of cardiac functional impairment. B-type natriuretic peptide (BNP) increases in response to volume or pressure overload in the heart. Several studies have evaluated the value of natriuretic peptides in the diagnosis and prediction of cardiotoxicity induced by anticancer drugs. After initial findings in 1998, a large number of clinical studies evaluated BNP in patients with various malignancies (hematologic and solid tumors) and of different ages (children and adults), receiving chemotherapy. All these studies reached similar conclusions and found that persistent elevations of BNP were associated with reduced cardiac tolerance to cardiotoxic agents (see review in reference 74). Most authors found an association between increased levels of natriuretic peptides and cardiac dysfunction. However, few reports looked at the possible use of this biomarker for the early stratification of patients at risk of cardiac dysfunction. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was evaluated as an early predictive marker of cardiac dysfunction in patients with aggressive malignancies receiving high-dose chemotherapy. In 67% of patients, NT-proBNP concentration remained unchanged or only transiently increased during a 72-hour period after chemotherapy. In all these patients, no significant echocardiographic changes were recorded during a 12-month follow-up.

The remaining 33% of patients showed persistently increased NT-proBNP concentrations, which were still elevated at 72 hours; these patients had a significant worsening of both diastolic and systolic parameters during the following months of observation. In this group, LVEF decreased from 63% to 45% (P<0.001). A strong relationship was also found between NT-proBNP value at 72 hours and LVEF changes at 12 months versus baseline evaluation (before chemotherapy) (Figure 3).

More recent studies confirmed that the administration of anticancer drugs and continuous rise in BNP are associated with chemotherapy-induced cardiac toxicity. However, BNP levels can vary considerably depending on the physiological characteristics of the patient, which makes it difficult to establish cutoff values for the general population. Several studies found that BNP had fairly poor sensitivity for detecting asymptomatic decreases in LVEF. Measurement of natriuretic peptides may thus represent a very promising strategy for monitoring cardiac function or detecting subclinical damage, allowing identification of those patients needing further cardiac assessment. However, although BNP might be beneficial for early identification of high-risk patients who require treatment or change of chemotherapeutic strategies, these biomarkers cannot currently substitute imaging modalities for measurement of LVEF, and further validation is needed prior to their use on a large scale and inclusion into anticancer protocols.

Other proposed biomarkers

Other chemotherapy-related cardiac toxicity biomarkers have been proposed such as fatty acid binding protein, glycogen phosphorylase isoenzyme BB, and inflammatory cytokines, especially interleukin 6 (IL-6). However, although these markers are highly sensitive and rapidly released after acute myocardial ischemia, they are less specific than troponin in detecting cardiac damage from causes other than ischemia.

Several clinical studies have also analyzed biomarkers of endothelial damage in cancer patients. Long-term cancer survivors treated with chemotherapy showed increased markers of endothelial injury. Late endothelial dysfunction can contribute to the accelerated athero-
sclerotic process, leading to an increased risk for future CVD. However, at present, no correlation with long-term cardiovascular events has been demonstrated, and the predictive role of these markers is still unknown.

**PREVENTION OF CARDIOTOXICITY: POSSIBLE STRATEGIES FOR CARDIOPROTECTION**

Several preventive measures are currently recommended during cancer chemotherapy, including close monitoring of cardiac function, reduction in cumulative chemotherapy dose, and use of anthracycline analogs, nutritional supplements, and preventive pharmacological treatments in high-risk patients identified by means of biomarkers. Several strategies for selective cardioprotection have been explored and have shown varying degrees of success. Extending infusion duration is clearly cardioprotective, but requires infusion pumps and indwelling catheters. Dexrazoxane, an iron chelator, is highly protective against anthracycline-associated cardiotoxicity. However, there is no evidence in support of a difference in response rate or survival between the dexrazoxane and control groups. The results for adverse effects were ambiguous. Concerns have also been raised regarding possible impairment of oncologic efficacy by dexrazoxane, and there is no widespread acceptance in the routine management of patients treated with anthracyclines.

Experimental models suggest that the cardiac renin-angiotensin system plays an important role in the development of chemotherapy-induced cardiomyopathy and that treatment with angiotensin-converting enzyme (ACE) inhibitors may reduce anthracycline cardiotoxicity. Increased oxidative stress has been suggested as a possible primary mechanism of cardiotoxicity, and ACE inhibitors have been shown to exert antioxidant effects by scavenging free radicals. Carvedilol has also been proposed as a cardioprotective agent against anthracyclines. In a recent randomized study, prophylactic use of carvedilol in a small population of patients treated with anthracyclines prevented left ventricular dysfunction and reduced mortality. Further large randomized clinical trials are certainly warranted to confirm this result.

There is no clear recommendation for prophylactic anticoagulation strategy in patients undergoing chemotherapy. Although there is a risk of thromboembolic complications, it appears to be relatively low. It thus seems reasonable to consider aspirin therapy in selected patients undergoing chemotherapy.

There is conflicting evidence regarding a possible beneficial effect of aerobic exercise in reducing anthracycline cardiotoxicity in patients with breast cancer. A recent meta-analysis of 16 studies examining the efficacy of aerobic exercise to prevent (before and during therapy) and/or treat (after therapy) doxorubicin-induced cardiotoxicity suggested that exercise prevents doxorubicin-induced impairment in LV systolic and diastolic function. However, contrary to prior reports and preclinical data, a recent phase 2 trial in which patients were randomized to doxorubicin-cyclophosphamide alone or doxorubicin-cyclophosphamide in combination with supervised endurance exercise training (3 times per week, 60% to 100% of baseline VO2 peak) for 12 weeks failed to evidence any significant changes in echocardiographic measures in either group, from baseline to 12 weeks, although the doxorubicin cyclophosphamide–induced increase in atrial natriuretic peptide was attenuated by exercise training.

Thus, at present, the most appropriate and effective type of exercise for preventing and/or treating anthracycline-induced cardiotoxicity remains unknown.

**HOW TO MONITOR CARDIAC FUNCTION AND DETECT EARLY HEART FAILURE**

There is still no established consensus about cardiac monitoring during chemotherapy. During breast cancer therapy, it is recommended to assess LVEF: (i) before starting anthracycline treatment; (ii) before starting trastuzumab; (iii) every 3 to 6 months during treatment; and (iv) every 6 to 12 months for at least 2 years following cessation of treatment. If trastuzumab is withheld because of a reduction in ventricular function, LVEF should be assessed more frequently. When trastuzumab is used without an anthracycline, less intensive monitoring is acceptable. With other agents and regimens, protocols are less clear.

All patients considered for chemotherapy should undergo thorough cardiovascular evaluation, as part of routine oncologic evaluation. Patients with a history of heart failure or arrhythmias should undergo cardiac evaluation prior to initiation of chemotherapy. Patients considered for chemotherapy should have a baseline electrocardiogram to detect conduction block, arrhythmias, or repolarization abnormalities. Serial assessment of left ventricular function is warranted in patients in whom treatment with anthracyclines, trastuzumab, tyrosine kinase inhibitors, or anthracyclines is being considered, although standards for surveillance screen-
ing intervals have not been established. At least one baseline assessment and one repeat evaluation of left ventricular function after administration of a total dose of >150 mg/m² of doxorubicin should be done, although recommendations vary widely in the literature. Similar recommendations for screening intervals of cardiac function with trastuzumab cannot be made, as cardiotoxicity may occur in a non–dose-dependent fashion.\textsuperscript{100}

Routine assessment of cardiac function, even in asymptomatic individuals, is helpful, as there is evidence that in asymptomatic patients the discontinuation of cardiotoxic chemotherapy when left ventricular systolic dysfunction is first identified might allow for reversible improvement in cardiac function.\textsuperscript{101} Routine evaluation of cardiac biomarkers, including troponin I and BNP, should be considered in patients undergoing chemotherapy with cardiotoxic agents such as anthracyclines.

**FOLLOW-UP OF PATIENTS RECEIVING ANTIANGIOGENIC AGENTS**

There is a paucity of data to guide management of angiogenesis inhibitor–associated hypertension. A recent assembly of the Cardiovascular Toxicities Panel of the National Cancer Institute set a goal of 140/90 mm Hg (and 130/80 mm Hg in patients with chronic kidney disease or diabetes mellitus). However, in most oncological clinics, hypertension is often neglected in patients without clinical signs. The most commonly prescribed antihypertensive drugs are ACE inhibitors and/or calcium blockers, and these are able to normalize blood pressure, alone or in combination, in a large majority of patients. Sunitinib and sorafenib are metabolized by the CYP3A4 system, so nondihydropyridine calcium channel blockers (verapamil and diltiazem), which are CYP3A4 inhibitors, should be avoided in patients on these agents, but may be considered in patients on bevacizumab. Antiangiogenic dose reduction or withdrawal may need to be considered in case of severe refractory hypertension or hypertensive crisis.

Particular attention must be paid to the few days following administration of angiogenesis inhibitors as a transient increase in blood pressure is often observed. Rapid titration of antihypertensive therapy must be achieved in the first week after angiogenesis inhibitor initiation. Home blood pressure monitoring facilitates adaptation of titration of antihypertensive treatment. To avoid hypotension, blood pressure should be closely monitored, and antihypertensive medications should be down titrated when angiogenesis inhibitor therapy is stopped.

**THE CHALLENGES OF DELIVERING CARDIAC CARE**

During cancer treatment, the attention of patients and their families is primarily focused on cancer care even if patients have serious comorbid conditions such as diabetes or cardiac disease.\textsuperscript{102} Because of the frequent oncology follow-up visits, other health care visits are often postponed or neglected. Furthermore, heart failure symptoms, such as fatigue, exertional dyspnea, and lower-extremity edema are very similar to the expected adverse effects of cancer therapy and may delay or mask the diagnosis of heart failure in these patients.

Lack of communication among specialists, especially those in different institutions, easily results in fragmented care. Multispecialty groups combining cardiovascular and cancer care are rare. Diagnosis of cancer and initiation of treatment by an oncologist may result in a delay in diagnosis and treatment of coronary artery disease, which may be exacerbated by treatment-induced hypertension, ischemia, or heart failure. Often patients themselves, especially pediatric cancer survivors, have no specific knowledge of their treatment and its late toxic effects. Long-term follow-up by oncologists primarily focuses on disease recurrence, and nononcologists cannot be expected to know every single specific cardiac toxicity risk attached to every single type of cancer treatment. To anticipate this problem, survivorship clinics that provide annual surveillance for late effects of cancer treatment are becoming more prevalent in many academic cancer centers. However, fewer than 1 in 8 patients with cancer are estimated to be admitted to academic medical centers in the United States, and most new cancer cases continue to be treated in hospitals and physician offices located close to the patient’s home. Survivors receive most of their care from a primary care provider.\textsuperscript{103} Improved awareness is thus required, such as provided by the International Cardio-Oncology Society, a group committed to improving care in patients with cancer and cardiac disease.\textsuperscript{104}

**DEVELOPING A CARDIOLOGY-ONCOLOGY CLINICAL PRACTICE GUIDELINE (CPG)**

Clinical practice guidelines (CPGs) are generally developed by governmental authorities or professional societies.\textsuperscript{105} Often, multiple competing CPGs on a given topic coexist, and despite being drafted by recognized experts, are not always in agreement about the strength of a specific recommendation, generating
confusion and limiting its impact. Moreover, CPGs are often bulky documents, containing hundreds of recommendations. The time and effort required to produce a CPG is substantial and reflected in the many years that elapse between each update. It follows that it is an even more daunting task to produce a CPG that addresses two major medical problems pertaining to two different medical fields. Thus, existing CPGs for the prevention, diagnosis, and treatment of CVD in the cancer patient or, conversely, of cancer in the patient with CVD, are few and far between: although around 400 guidelines exist for CVD and even more for neoplasms, only a handful specifically address the patient with concurrent cancer and CVD.\textsuperscript{106}

\textbf{Why do we need a guideline?}

There are several reasons for developing a specific cardio-oncology CPG:

- Cardiovascular adverse effects of anticancer therapy are fairly common.
- CVD and cancer are likely to frequently coexist in the same patient, as both share many common risk factors.
- Cardiovascular comorbidities are common, associated with increased mortality in patients with cancer, and may affect diagnostic and therapeutic options.
- CVD, existing before or resulting from anticancer therapy, may adversely affect survival and quality of life.
- Oncology and cardiovascular specialists may not be familiar with most current therapies and guidelines in the other specialty.
- Treatment of patients with both CVD and cancer with 2 separate CPGs may result in more adverse effects, more complicated therapy, greater costs, and poorer outcomes.
- The best survival and quality of life for cancer patients with CVD, either preexisting or resulting from anticancer therapy, is likely to occur when guidelines for therapy are shared by both treating oncologists and cardiologists.

\textbf{Potential problems for a guideline}

Health care providers dealing with patients with cancer and CVD must be knowledgeable about at least six main topics: left ventricular dysfunction, rhythm management (particularly atrial fibrillation and arrhythmias associated with QT prolongation), myocardial ischemia, hypertension, cardiac risk assessment and management (chemotherapy and cancer surgery), and survivorship. Therefore, these topics must be part of medical training from the very first exposure to clinical medicine.\textsuperscript{107} Early identification of patients at risk for cardiotoxicity is a priority for cardiologists and oncologists, in order to plan personalized antineoplastic therapeutic strategies, provide support of cardiac function, and monitor progression of cardiac damage.

\section*{CONCLUSION}

Patients with cancer run a substantial risk of developing heart disease induced by chemotherapy and radiation therapy. With the advent of new complex chemotherapeutic protocols and the increased incidence of CVD, much greater dialogue between cardiologists and oncologists is required for optimal patient care.

Better understanding of onco-cardiology or cardio-oncology is critical for effective care of the cancer patient. Much work has been done to characterize the toxicity of drugs used in cancer therapy, but further research is needed on long-term outcomes and preventive and treatment strategies. Avenues for prevention and early treatment of cardiotoxicity are available, but under-explored. A multidisciplinary approach is needed to foster communication between health care providers and ensure optimal patient outcomes, so as to avoid today's cancer survivors becoming tomorrow's heart patients.

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Cardiac disease and heart failure in cancer patients: is our training adequate to provide optimal care?
What is the role of the Notch pathway in cancer treatment–induced cardiotoxicity?

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Cancer mortality has been steadily decreasing in recent years due to aggressive prevention strategies and the development of treatments tailored to specific types of cancer. Some of these treatments, including not only chemotherapeutic drugs, but also targeted drugs like trastuzumab, are associated with cardiotoxicity that can be so severe as to cause death. Even though the mechanisms of cardiotoxicity are not fully understood, it is becoming clear that some cancer treatments have detrimental effects on survival of cardiomyocytes and cardiac endothelial cells. Notch is a key pathway involved in modulating proliferation and survival of both these cell types. Better understanding of how this pathway is affected by cancer treatments could lead to the development of new protocols to limit or reduce cancer therapy–associated cardiotoxicity.

The development of new therapeutic strategies for many types of cancers has prolonged the cancer-free survival time of an increasing number of patients. Unfortunately, cardiotoxicity is an important side effect of many oncology drugs. Depending on drug type, between 5% and 25% of cancer patients develop heart failure defined as a reduction in left ventricular ejection fraction (LVEF) in the range of 10% to 55%, without accompanying signs or symptoms, that can progress to cause patient death.1-3

Early detection of cardiotoxicity from oncologic treatment is crucial to set up a strategy to prevent irreversible cardiac damage and heart failure. Left ventricular function assessed by LVEF is well established as a strong predictor of cardiac morbidity and mortality in general. However, LVEF is not sensitive enough to reveal subclinical myocardial dysfunction, which can lead to symptomatic congestive heart failure and death.4

Since there are no available markers of early cardiotoxicity, the oncologist lacks effective tools to prevent or limit cardiac damage associated with cancer therapy. Understanding the molecular mechanisms behind heart dysfunction caused by cancer treatment could lead to the identification of biomarkers for early detection of cardiotoxicity and the development of new therapeutic strategies to block the onset and progression of heart failure.

The majority of studies on cancer treatment–induced cardiotoxicity focus on the effects of chemotherapeutic and biological agents on cardiomyocyte survival.1-3 However, the effects on myocardial endothelial cells should also be considered. Antiangiogenic agents, which are becoming widely used for their inhibitory effect on tumor vasculature, could also affect endothelial cells in myocardium, with consequent ischemia.5

**Selected Abbreviations and Acronyms**

- ADAM: A disintegrin and metalloprotease
- GSI: gamma secretase inhibitor
- HER2: human epidermal growth factor receptor-2
- HUVEC: human umbilical vein endothelial cells
- LVEF: left ventricular ejection fraction
- NIC: Notch intracellular fragment
- PDGF: platelet-derived growth factor
- VEGF: vascular endothelial growth factor

**Keywords:** apoptosis; cancer treatment; cardiomyocyte; cardiotoxicity; endothelial cell

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An understanding of how oncology drugs modulate crucial pathways controlling survival of both endothelial cells and cardiomyocytes is the key to developing strategies to prevent cancer therapy–induced cardiotoxicity. This review focuses on the Notch pathway, a pathway that plays a key role in controlling cardiomyocyte and endothelial cell proliferation and survival. The interactions between the Notch pathway subunits are held together on the cell membrane by noncovalent bonds. Binding of ligand present on an adjacent signaling cell triggers the removal of the extracellular subunit by A disintegrin and metalloprotease (ADAM) followed by an intramembranous cleavage by γ-secretase, a multisubunit membrane protease. These two proteolytic cuts release an intracellular domain, which is the active form of Notch (NIC, Notch intracellular fragment). NIC translocates into the nucleus, where it modulates transcription in the receiving cells via RBP-Jκ (recombinant signal binding protein 1 for Jκ) transcription factor (Figure 1). The most prominent Notch target genes are the Hes and Hey gene family, which are negative regulators of transcription. While Hes genes are crucial in neural and endocrine functions, Hey genes play a crucial role in the cardiovascular system. Very little is known about the molecular target and interaction of these genes. Other well-known Notch targets include p21Cip/Waf, cyclin D1, cyclin A, and transcription factors of the nuclear factor–κB (NF-κB) family. Nevertheless, the set of directly and indirectly Notch-regulated genes and proteins is very large and new targets are still being discovered. The result of Notch activation is cell-context dependent and the output is strongly affected by timing, duration, and dose of activation. This tight regulation is accomplished by posttranslational modifications such as phosphorylation, glycosylation, and by rapid ubiquitination-mediated degradation. Inflammatory cytokines also modulate Notch activity as well as cross talk with other key pathways such as NF-κB, estrogen receptor alpha, and vascular endothelial growth factor (VEGF) receptors.

**NOTCH AND ENDOTHELIAL CELL SURVIVAL**

The role of the Notch pathway in the development of the vascular system is well established. Mouse embryos carrying mutations inactivating Notch 1 or both Notch 1 and Notch 4 show severe vascular defects and are not viable. Molecular data indicate that during development, Notch acts mainly by determining arterial-venous specification. Notch receptors 1, 2, and 4 and ligands Dll1, 4 and Jagged 1, 2 are ex-
pressed in the endothelium also during adult life and modulate postnatal angiogenesis. According to the widely accepted model, under ischemic conditions, the formation of new blood vessels is driven by VEGF-A, which induces endothelial cell sprouting from the parent vessels, followed by migration, proliferation, and tube formation. Notch activity, also induced by VEGF-A, modulates angiogenesis by limiting the number of sprouts through inhibition of the VEGF receptor, and interfering with Notch signaling leads to dysregulated and unproductive angiogenesis. Thus, in the context of angiogenesis, VEGF is the driving force, whereas Notch can be considered the steering wheel.

Beyond angiogenesis, Notch also plays an important role in protecting endothelial cells from apoptosis induced by conditions such as inflammation, oscillatory blood flow, and ischemia. In vitro treatment of endothelial cells with inflammatory cytokine tumor necrosis factor α (TNF-α) leads to dysregulation of Notch signaling and apoptosis. A prominent role in particular for Notch 4 in protection of endothelial cells has been shown in cardiac allograft vessels in which impaired Notch 4 expression caused by proinflammatory cytokines promotes endothelial cell dysfunction and transplant arteriosclerosis. Notch dysregulation could be causing the observed increase in apoptosis of human umbilical vein endothelial cells (HUVEC) exposed to serum from heart failure patients. It is well known that serum from these patients is characterized by an inflammatory imbalance with levels of TNF-α increasing with the worsening of the disease.

Disturbed blood flow conditions existing in regions of artery bifurcation predispose the endothelium to atherosclerotic plaque formation by reducing expression of protective genes, which leads to increased endothelial cell apoptosis. Accordingly, inhibition of the survival pathway NF-κB has been observed in artery sites prone to plaque formation. Exposure of microvascular endothelial cells to high–laminar flow conditions (protective for the endothelium) results in upregulation of Notch 1, which increases cell survival by upregulating the anti-apoptotic protein Bcl-2.

Under ischemic conditions, VEGF-A promotes not only migration and proliferation, but also protection, of endothelial cells from apoptosis. Cultures of HUVEC grown in the absence of serum to mimic an ischemic environment have shown that treatment with VEGF-A is unable to protect cells from serum deprivation–induced apoptosis in the absence of functional Notch 1 signaling. These studies clearly demonstrate that an active Notch pathway is necessary for optimal survival of the endothelium (Figure 2).

**Figure 2.** Notch activation protects endothelial cells from apoptosis caused by different types of insult. Endothelial cell apoptosis and consequent vascular endothelium dysfunction are the first steps of the formation of the atherosclerotic plaque.

**NOTCH AND CARDIOMYOCYTE SURVIVAL**

Gene-targeted studies conducted in mice have attributed a precise role to Notch target genes Hey 1 and Hes 1 in the formation of the atrioventricular canal and during cardiac neural crest development. Consistent with these observations indicating a major role played by Notch during heart development, mutations in the Notch signaling pathway have been identified in human congenital defects such as Alagille syndrome, bicuspid aortic valve disease, and calcification of heart valves. Although these studies demonstrate the need for functional Notch signaling in heart development, we are only now beginning to understand the role of...
the Notch pathway in cardiomyocyte biology after birth. Stem cell precursors of cardiomyocytes express high levels of Notch 1, and active Notch signaling is required for their proliferation. Rat neonatal cardiomyocytes isolated at birth also express high levels of Notch 1 and are actively proliferating. After several passages in culture, Notch 1 expression in cardiomyocytes becomes undetectable and these cells lose their proliferative ability. These data indicate that Notch signaling is required for expansion of cardiac stem cells and immature cardiomyocytes, but that Notch needs to be switched off to achieve terminal differentiation. In agreement with this observation, in sections of adult rat myocardium, Notch signaling in cardiomyocytes is absent under normal physiological conditions, but becomes transiently reactivated in cardiomyocytes following myocardial infarct. In a rat model of Notch 1 haploinsufficiency, myocardial infarction scarring is more extensive in comparison with scarring in wild type animals, suggesting that Notch 1 signaling reactivation following ischemic insult could be a protective mechanism of cardiomyocyte survival. Consistent with this hypothesis, Notch 1 activation in cardiomyocytes in ischemic heart induces Akt activation, a pathway linked to cell survival. Prolonged Notch activation in mature cardiomyocytes may have different consequences. Campa et al have shown that forced activation of Notch in mature cardiomyocytes is associated with cell cycle progression block and apoptosis, indicating that prolonged and uncontrolled Notch activation can be lethal for these cells. Taken together, these data indicate that while Notch signaling is required for proliferation of cardiac stem cells and survival of cardiomyocytes, timing and dosing of activation have to be tightly controlled to avoid negative effects on cell survival (Figure 3 A and B).

**NOTCH AND ANTHRACYCLINE**

The anthracycline doxorubicin is effective in the cancer setting, but its clinical use is limited by cardiotoxicity, which has irreversible consequences beyond the dose of 500 mg/m². Although the mechanism of cardiotoxicity induction by anthracyclines is not fully understood, several observations suggest that interaction of these drugs with iron plays an important role. Anthra-

![Figure 3 (A and B). Notch signaling controls proliferation of cardiac stem cells and immature cardiomyocytes.](image-url)

- **A.** In terminally differentiated cardiomyocytes, Notch signaling is reduced and it becomes activated following an ischemic insult, conferring apoptosis protection. **B.** Prolonged activation of Notch in mature cardiomyocytes leads instead to apoptosis.
cyclines form a complex with iron, which catalyzes free radical production and leads to membrane disruption, widespread cellular dysfunction, and ultimately cardiomyocyte death with consequent strong inflammatory response, which enhances cardiac damage. Oxidative stress and inflammation are therefore hallmarks of anthracycline-induced cardiotoxicity.3

The Notch pathway is a major modulator of inflammation. Notch inhibition reduces reperfusion injury following ischemic stroke by limiting the inflammatory response as measured by reduced levels of interleukin 6 (IL-6) in serum and reduced number of inflammatory cells in damaged tissue.21 In atherosclerotic plaques of patients with carotid occlusion, activation of Notch 3/Dll4-mediated signaling in macrophages leads to expression of genes related to plaque instability and production of inflammatory cytokines.22

In the context of cancer treatment, specific clinical studies should determine whether cycles of combined treatment of doxorubicin and a Notch inhibitor could help reduce cardiotoxicity associated with anthracycline treatment.

**NOTCH AND HER2 INHIBITORS**

About 25% to 30% of all breast cancers overexpress HER2 (human epidermal growth factor receptor 2), a member of the epidermal growth factor receptor family involved in modulation of cell proliferation and survival.23 Trastuzumab is a humanized monoclonal antibody that interferes with HER2 receptor. When administered with paclitaxel or anthracyclines in patients with metastatic HER2-overexpressing breast cancer, trastuzumab prolongs disease-free survival compared with chemotherapy alone. Trastuzumab treatment causes heart failure and asymptomatic decline in systolic function in 22% to 25% of patients when administered sequentially or in combination with anthracyclines.23 Similarly to breast cancer cells, cardiomyocytes express HER2, which activates survival pathways in response to stressors. According to some authors, trastuzumab-induced cardiotoxicity results from exacerbation of anthracycline toxicity, since inactivation of HER2 in cardiomyocytes impairs their ability to repair anthracycline-induced damage.3 On the other hand, use of trastuzumab alone or in combination with paclitaxel is also associated with cardiotoxicity, even though this occurs in a smaller number of patients.24 Furthermore, differently from anthracyclines, trastuzumab-induced cardiotoxicity is reversible when treatment is interrupted. These observations show that further studies are needed to fully elucidate the molecular mechanism of trastuzumab-induced cardiotoxicity.

In vitro treatment of metastatic breast cancer cells overexpressing HER2 with trastuzumab increases the levels of Notch activity.25 Considering the role played by Notch in cardiomyocyte survival, it would be of great interest to investigate the effects of combination treatment with doxorubicin (the anthracycline used for breast cancer) and trastuzumab on Notch pathway in cardiomyocytes. If trastuzumab treatment leads to activation of Notch in these cells, then this sustained and uncontrolled activation of Notch signaling would synergize with doxorubicin in inducing cardiomyocyte apoptosis and therefore cardiotoxicity (Figure 4).
NOTCH AND ANTIANGIOGENIC DRUGS

Interference with tumor angiogenesis is a new promising avenue for cancer therapy. VEGF and platelet-derived growth factor (PDGF) receptors are the major players promoting tumor angiogenesis and an increasing number of drugs blocking these receptors in cancer cells are starting to be used in the clinic. Sunitinib, a small-molecule tyrosine kinase inhibitor that interferes with the activity of both VEGF and PDGF receptors, is widely used for treatment of patients with metastatic renal cell carcinoma and gastrointestinal stroma tumor. Similarly to the other drugs described so far, treatment with sunitinib causes cardiotoxicity in approximately 11% to 20% of treated patients. As with trastuzumab, the molecular mechanism by which this agent induces cardiotoxicity is still unknown.

Since endothelial cells line the entire circulatory system, the consequences of inhibiting VEGF signaling in the vasculature should be carefully evaluated in order to exclude diminished endothelial cell viability in the myocardium liable to result in ischemia. As discussed above, VEGF receptor cross talk with Notch signaling in endothelial cells and inhibition of VEGF receptor could lead to Notch downregulation, thereby increasing susceptibility of these cells to apoptosis (Figure 5).

POTENTIAL CARDIOTOXICITY OF NOTCH INHIBITORS

Gamma secretase inhibitors (GSI) are small molecules that interfere with the activity of γ-secretase, the enzyme required for Notch activation. The Notch pathway has been found to be activated in the majority of solid tumors and leukemias, where it inhibits treatment-induced cancer cell apoptosis. There are several ongoing clinical trials to evaluate the safety and efficacy of GSI used in combination with standard treatments. Intestinal toxicity has been observed in GSI-treated patients since Notch regulates the balance between secretory and absorptive cell types in the intestine. Considering the extensive involvement of Notch in the homeostasis of the cardiovascular system, possible cardiotoxicity associated with GSI treatment should be addressed by specifically designed preclinical studies and clinical trials with long follow up.

CONCLUSIONS

Cardiotoxicity is a serious side effect associated with many oncology drugs, which may hinder the success of cancer treatment. A clear understanding of the molecular mechanisms underlying cardiotoxicity induced by oncology drugs could help not only to reduce the rate of toxicity, but also to limit damage. The Notch pathway is an important modulator of cardiovascular cell function. The effects on this pathway of existing and experimental cancer treatments should therefore be carefully studied.

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Mortality and morbidity have been significantly reduced in many types of cancer thanks to the development of effective cancer therapies. Treatment of oncologic patients includes drug therapy, radiation therapy, and surgery. These treatment modalities often generate adverse cardiovascular complications affecting quality of life and prognosis. The most commonly used noninvasive method to monitor cardiotoxicity in patients receiving cancer therapy is echocardiography. It can be readily used to identify the most common forms of cardiac complications of cancer therapy, including left ventricular dysfunction, valvular dysfunction, and pericardial disease. Furthermore, advanced ultrasound techniques may be useful in the early detection of subclinical myocardial dysfunction.

Keywords: anthracycline; cancer therapy; cardiotoxicity; coronary artery disease; echocardiography; radiation; speckle-tracking; strain; trastuzumab; ventricular function

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What are the best tools for early diagnosis of cancer treatment–induced cardiotoxicity and what is the treatment?

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Oslo University Hospital - Rikshospitalet - Oslo - NORWAY

Mortality and morbidity have been significantly reduced in many types of cancer thanks to the development of effective cancer therapies. Treatment of oncologic patients includes drug therapy, radiation therapy, and surgery. These treatment modalities often generate adverse cardiovascular complications affecting quality of life and prognosis. The most commonly used noninvasive method to monitor cardiotoxicity in patients receiving cancer therapy is echocardiography. It can be readily used to identify the most common forms of cardiac complications of cancer therapy, including left ventricular dysfunction, valvular dysfunction, and pericardial disease. Furthermore, advanced ultrasound techniques may be useful in the early detection of subclinical myocardial dysfunction.

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Dialogues Cardiovasc Med. 2013;18:30-37
patients receiving potentially cardio
toxic cancer therapy includes cardi-
ologic examination, electrocardio-
graphy (ECG), and echocardiography.
In recent years, biomarkers such as
troponins,\textsuperscript{4,5} natriuretic peptides,\textsuperscript{5,6}
and high-sensitivity C-reactive pro-
tein\textsuperscript{7} have been introduced as po-
tential tools for monitoring cardiac
function. Endomyocardial biopsy is
also an accurate tool to detect car-
diotoxicity, but its invasive nature
may lead to serious complications.
At present, echocardiography is the
method of choice for noninvasive
cardiac evaluation in patients receiv-
ing cancer therapy, since LV systolic
and diastolic function, pericardial
disease, myocardial damage, and
valvular function can all readily be
assessed by this method.

This article discusses different meth-
ods for their ability to detect car-
diotoxicity and the therapeutic
modalities available for the preven-
tion and treatment of cancer ther-
apy–induced cardiac adverse events.

**CANCER THERAPY–
INDUCED CARDIOTOXICITY**

There are two types of chemother-
apy-induced cardiotoxicity—irre-
versible (type 1) and reversible
(type 2). Type 1 cardiotoxicity is
characterized by irreversible myo-
cardial damage, most commonly
evidenced in patients treated with
anthracyclines. About 60% of pedi-
atric cancer patients receive an
anthracycline, and 10% of these patients develop symptomatic car-
diomyopathy up to 20 years after the
end of chemotherapy.\textsuperscript{8,9} The risk of cardiomyopathy increases with
higher cumulative anthracycline
doses: 3% for doses of 400 mg/m\textsuperscript{2},
7% for doses of 550 mg/m\textsuperscript{2}, and
18% for doses of 700 mg/m\textsuperscript{2}.\textsuperscript{11} The
earliest alteration in this type of
cardiotoxicity is myofibrillar disor-
ganization, progressing to myocyte
apoptosis and necrosis. When heart
failure occurs, the clinical picture
may stabilize, but damage seems to
be permanent and irreversible.

Type 2 cardiotoxicity is most fre-
quently evidenced in patients treat-
ed with trastuzumab.\textsuperscript{10,11} Trastuzu-
mab is a recombinant monoclonal
antibody that binds selectively to
the human epidermal growth fac-
tor receptor 2 (HER2) protein. The
drug was approved by the US Food
and Drug Administration in 1998
for treatment of breast cancer that
overexpresses HER2, which occurs
in approximately 20% to 25% of hu-
man breast cancers.\textsuperscript{12} Addition of
trastuzumab to chemotherapy elic-
tits an improvement in the rate of
overall survival among patients with
first-line metastatic disease by
30%.\textsuperscript{12} Unlike anthracycline toxicity,
trastuzumab does not seem to cause
myocyte loss. Myocytes appear his-
tologically normal, but alteration
may be detected by using electron
microscopy, consistent with revers-
ible cardiomyopathy.\textsuperscript{13} It is not dose-
dependent and is reversible if ther-
apy is withdrawn. Furthermore, the
drug can be safely readministered
after recovery of EF.\textsuperscript{11} Development
of heart failure during treatment
with trastuzumab is seen in approx-
imately 5% of patients receiving
adjuvant chemotherapy if there are
no risk factors for heart failure.\textsuperscript{14}
Importantly, occurrence of cardiac
dysfunction increases significantly
when trastuzumab is used in com-
bination with anthracyclines, and
can be as high as 27%.\textsuperscript{12}

Cardiovascular toxicity induced by
cancer therapy manifests as preclini-
cal or clinical events. Preclinical
toxicity may be assessed noninva-

cessively by biochemical techniques
and advanced echocardiographic
methods or invasively by histo-
pathological techniques after en-
domyocardial biopsy. A recent and
comprehensive grading system has
been developed by the National
Cancer Institute, which takes into
account all the important clinical
and laboratory changes.\textsuperscript{15,16}

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**Table I. Cancer therapy–induced cardiac side effects.**

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Cancer therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular</td>
<td>Anthracyclines, cyclophosphamide, ifosfamide, mitomycin, cytarabine, paclitaxel, alemtuzumab, bevacizumab, trastuzumab, interferon-α, all-trans retinoic acid, imatinib, pentostatin</td>
</tr>
<tr>
<td>dysfunction</td>
<td></td>
</tr>
<tr>
<td>Valvular disease</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Pericardial disease</td>
<td>Busulphan, cyclophosphamide, cytarabine, all-trans retinoic acid, imatinib, radiation therapy</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>Cisplatin, capecitabine, vinca alkaloids, interferon-α, interleukin 2, 5-fluorouracil, radiation therapy</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Ifosfamide, paclitaxel, rituximab, interleukin 2, arsenic trioxide, thalidomide</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Etoposide, paclitaxel, alemtuzumab, cetuximab, rituximab, interleukin 2, denileukin, interferon-α, all-trans retinoic acid, homoharringtonine</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Bevacizumab, cisplatin, interferon-α</td>
</tr>
<tr>
<td>Endomyocardial fibrosis</td>
<td>Busulphan</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>Bevacizumab, paclitaxel, thalidomide</td>
</tr>
</tbody>
</table>

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Cancer treatment–induced cardiotoxicity: diagnosis and treatment - Edvardsen and Sarvari
Exposure to cardiotoxic chemotherapeutic agents is an indication for baseline and subsequent reevaluation of cardiac function according to the guideline update for clinical applications of echocardiography by the American Society of Echocardiography. Baseline EF and subsequent imaging studies of LV function are required before considering additional chemotherapy doses. Importantly, chemotherapy termination is based on specific criteria of changes in LV function. However, there is no agreement on the optimal method of monitoring anthracycline-induced cardiotoxicity. The lack of a generally accepted and used guideline is reflective of conflicting data.

Cardiotoxicity of cancer therapy and LV function

- **Two-dimensional echocardiography.** The most common noninvasive method of monitoring cardiotoxicity induced by chemotherapeutic agents and radiation therapy is echocardiography (Figure 1). It can readily identify the main forms of cardiac diseases in cancer patients, including systolic and diastolic LV dysfunction, heart valve disease, and pericardial disease. Currently, left ventricular ejection fraction (LVEF) is the most widely used measure for detection of early LV dysfunction after administration of chemotherapeutic agents. Although LVEF is a well-established and strong predictor of cardiac morbidity and mortality, it presents a number of challenges related to image quality, assumptions of LV geometry, expertise, and is limited to assessment of changes in ventricular cavity size during the cardiac cycle. This traditional volume-based echocardiographic parameter provides an indirect assessment of myocardial function, and is insensitive to early changes in cardiomyopathy. LV dysfunction may progress to overt congestive heart failure, therefore early detection and treatment of cardiotoxicity is crucial in order to reduce the development of clinical manifestations.

- **Tissue Doppler imaging (TDI)** provides quantitative information on myocardial diastolic relaxation and systolic performance. Early changes
in LV function of cancer patients has been reported by TDI at multiple LV sites, both early and late after completed anthracycline therapy. Systolic and diastolic dysfunction can be present in these patients despite a normal LVEF (Figure 2). However, all tissue velocity measurements are susceptible to artifact from tethering and translational motion (ie, displacement of the entire heart is recorded as tissue motion of the specific segment being measured). In addition, TDI is angle dependent.

- **Two-dimensional speckle tracking echocardiography.** Recent studies have demonstrated that early detection of subclinical myocardial alterations could be achieved by two-dimensional speckle tracking echocardiography (2D-STE) (Figure 3). 2D-STE is a semiautomated, angle-independent, quantitative technique for assessment of cardiac function based on gray-scale images. Strain echocardiography has been introduced as an accurate tool for assessment of regional and global myocardial function and has been demonstrated to be more sensitive and accurate compared with conventional echocardiographic measures of systolic function such as radial directions. It is a measure of deformation, an intrinsic mechanical property, and measures myocardial systolic function more directly compared with conventional cavity-based echocardiographic measures. In a recent study, a decrease in longitudinal strain preceded decreases in EF in patients treated with anthracyclines. In another study, anthracycline-treated patients with normal LVEF had significantly lower LV function assessed by strain echocardiography compared with healthy individuals.

- **Diastolic LV function.** It is now recognized that diastolic dysfunction is also an early sign of cancer therapy–induced cardiac dysfunction in patients with normal LVEF (Figure 2). Diastolic function can be evaluated by combining the mitral inflow Doppler pattern and myocardial velocities assessed with TDI. Information on instantaneous LV diastolic function and filling pressures can be obtained by combining the ratio of the early mitral inflow and the early myocardial diastolic velocity (E/e’). Other diastolic parameters such as early peak flow velocity–to–atrial peak flow velocity (E/A) ratio, deceleration time, and isovolumic relaxation time have been reported to be impaired in more than 50% of patients treated with anthracyclines, even though LVEF was still normal. Thus, measurements of diastolic function by Doppler echocardiography may be a sensitive method for early detection of toxicity.

- **Stress echocardiography.** Exercise and dobutamine echocardiography has also been studied to assess early anthracycline cardiotoxicity. However, the results of these studies have been insufficient or controversial. Thus, the role of provocative-testing modalities in the early detection of subclinical cardiomyopathy is uncertain.

- **Three-dimensional echocardiography** has higher accuracy in the assessment of LV volumes and LVEF than two-dimensional echocardiography. Furthermore, it has good correlation.
with computed tomography (CT) and magnetic resonance imaging (MRI)-derived LV volumes, but the method is still hampered by inferior image quality compared with two-dimensional imaging. However, early myocardial alterations are not widely assessed with this method.

• **Cardiac MRI** offers the most accurate assessment of LVEF, and does not expose the patient to ionizing radiation. Late enhancement with gadolinium contrast may reveal early signs of injury such as myocardial fibrosis before reduced LVEF is apparent. However, cardiac MRI is expensive, not readily available and cannot be performed in patients with metal devices. Furthermore, gadolinium can be unsafe in patients with significant renal failure.

• **Biomarkers.** Troponin I and T may be useful in early detection of cancer therapy–induced cardiotoxicity before the development of a change in LVEF. Natriuretic peptides have been shown to be elevated in response to volume overload, and are useful in the diagnosis and treatment of heart failure. They may also be elevated in patients receiving cancer therapy even before the development of LV dysfunction assessed by LVEF. High-sensitivity C-reactive protein showed to be a promising marker of early trastuzumab-induced cardiotoxicity.

• **Nuclear imaging.** Historically, MUGA was the most frequently used modality for LV function monitoring in cancer patients. However, it only assesses LVEF and left ventricular size and involves ionizing radiation. Due to improvements in echocardiographic imaging, its use is now largely outdated. Nevertheless, LVEF measurements by nuclear imaging techniques are highly reproducible. In addition, recent advances in targeted molecular imaging with single-photon emission computed tomography and positron emission tomography may be able to detect cell death induced by anthracyclines.

Due to improvements in echocardiographic imaging, its use is now largely outdated. Nevertheless, LVEF measurements by nuclear imaging techniques are highly reproducible. In addition, recent advances in targeted molecular imaging with single-photon emission computed tomography and positron emission tomography may be able to detect cell death induced by anthracyclines.

**Cancer therapy and valvular disease**

There is frequent and progressive valvular deterioration during the first two decades after mediastinal radiation therapy with or without chemotherapeutic agents. Radiation causes fibrous thickening of cardiac valves, retraction, and calcification (Figure 1). Valve retraction is the predominant early change that causes regurgitation. Development of thickened, calcified valves that may finally result in stenosis may take as long as 20 years. The mean time from radiation to onset of symptoms is approximately 8 years. The valves on the left side are more often affected (Figure 4), probably due to the higher pressure. All valvular changes after cancer therapy can be readily diagnosed and monitored with echocardiography.

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**Cancer therapy and pericardial disease**

Pericardial disease after radiation or chemotherapy most commonly presents as pericardial effusion or pericarditis. Pericardial effusion is typically an early presentation, whereas pericardial fibrosis and constriction is a late one. These changes are often detected by coincidence by CT, ordered primarily for the follow up of the malignant disease. Acute complications such as cardiac tamponade cause dramatic hemodynamic compromise and need early diagnosis by echocardiography and immediate medical attention. Both acute and chronic anthracycline therapy can induce...
pericarditis and/or pericardial effusion, however the main cause is radiation therapy. Pericardial effusion size should be assessed by echocardiography for appropriate management. Pericardial fibrosis and constriction can be investigated by echocardiography, cardiac CT and MRI, and right heart catheterization, in order to differentiate it from restrictive cardiomyopathy.

**Cancer therapy and coronary artery disease**

A chronic complication such as silent progression of coronary atherosclerosis is difficult to recognize and may arise in cancer patients who do not have traditional risk factors for coronary artery disease. They may be asymptomatic, although new myocardial perfusion defects can be detected in approximately 50% of these patients. Obviously, patients with preexisting coronary artery disease are even more vulnerable since some chemotherapeutic agents (eg, capecitabine) and in particular radiation therapy are able to provoke accelerated coronary atherosclerosis. Clinically, most patients present with angina, dyspnea, or heart failure, although sudden death has also been reported. After radiation therapy, the mean interval for developing coronary artery disease is approximately 7 years.

According to a recent study, high coronary artery calcium scores by CT more than 15 years after mediastinal irradiation might identify patients with clinically significant coronary artery disease (Figure 5)."
or multiple chemotherapies. Therefore, the duration of cardiac monitoring should be long and accurate. When cardiotoxicity is suspected, strategies to prevent or reduce these adverse events should be initiated. Possible approaches include changing patterns of drug administration over time, reducing the total dose of the drug, changing the administration from rapid infusion to continuous infusion, and avoiding simultaneous administration of drugs that cause synergistic cardiotoxicity. These modifications may considerably reduce toxicity rates. Liposomal formulations may further decrease cardiotoxicity.

Dexrazoxane, a derivative of ethylenediaminetetraacetic acid (EDTA), reduces the amount of free iron in myocytes, thus reducing the number of metal ions complexed with anthracyclines and, consequently, decreasing the formation of superoxide radicals. It has been used to protect the heart against the cardiotoxic side effects of anthracyclines. However, since 2011 its use is restricted exclusively to adult patients with breast cancer who have received high doses of doxorubicin or epirubicin, while general approval for use for cardioprotection has been withdrawn due to clinical trials showing higher rates of secondary malignancies in pediatric patients. Furthermore, dexrazoxane may aggravate thrombocytopenia and granulocytopenia.

LV dysfunction induced by certain chemotherapeutic agents may be largely reversible with proper therapies, which include ceasing the administration of the agent, treating cardiac risk factors, and administering appropriate therapy for LV dysfunction. These principles apply to any cardiac toxicity, but especially to the management of heart failure. Neurohormonal antagonism by β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists is the basis of heart failure therapy and should be administered to cancer patients as aggressively as to any other patient population with signs of LV dysfunction. Cardiac toxicity can often be managed best by removing the offending agent. However, cancer therapy may not be the only explanation for newly developed LV dysfunction, therefore other reversible causes should be searched for.

Cancer therapy–induced ischemia is a reversible cause of LV dysfunction. Management of cancer treatment–induced coronary artery disease is similar to that of atherosclerotic disease and includes percutaneous coronary intervention and coronary artery bypass grafting. Since radiation induces mediastinal fibrosis, surgical bypass grafting may be difficult in these patients and is associated with a high incidence of complications. Medical treatment of cancer therapy–induced atherosclerosis includes statins, β-blockers, and acetylsalicylic acid.

CONCLUSION

A new cohort of patients has arisen due to advances in detection and therapy of cancer, and is becoming a major public health issue. As a consequence of improved survival, these patients will live long enough to develop cardiac complications of cancer therapy. Strategies for the reduction of cancer therapy–induced cardiotoxicity and early detection of its presence is vital. Although traditional echocardiography is still the method of choice for the follow-up of these patients, new echocardiographic techniques and biomarkers are promising novel methods for early detection of subclinical myocardial alterations.

Importantly, patients should always undergo thorough evaluation before potentially life-saving cancer therapy is stopped. The risk of recurrent cancer has to be carefully weighed against the risk of cardiovascular morbidity and mortality by cardiologists and oncologists at all times in patients receiving potentially cardiotoxic agents.

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The blood pressure curve is characterized by two different components: a steady component, corresponding to resistance microvessels and thus to mean arterial pressure and continuous flow; and a pulsatile component, corresponding to macrovessels and thus to pulsatile pressure and flow. These two vascular components are in constant interaction through numerous neurohumoral pathways and transit of wave reflections. Survival in cardiovascular diseases requires complex mechanisms including the totality of macrovessels and microvessels together with the cyclic movement of the heart. Continuous crosstalk between all these parameters is necessary in order to interpret the messages of cardiovascular disease and for cancer risk to be efficiently transmitted within the body.

The aorta originates in the left ventricle and almost immediately delivers branches to the heart, head, and upper and lower limbs (macrocirculation). Beyond these early branches, the total cross-sectional area of the arterial tree increases markedly. But whereas total cross-sectional area increases, the average diameter is reduced, indicating that there is an increased number of bifurcations leading to arterioles (microcirculation). All along the vascular tree, the forces responsible for flow are exclusively governed by the pressure generated by the heart. This parameter, which is the difference between the actual pressure and its hydrostatic component, is commonly referred to as “blood pressure” (BP). It is the gradient of excess pressure that drives the flow. The distribution of this excess pressure through the circulation, which is largely dissipated in forcing the blood through the microcirculation, is at the origin of vascular resistance. A distinctive feature is that the heart acts as an intermittent, and not a steady, pump. Increased vascular resistance is considered the most classic hallmark of hypertension. The behavior of vascular resistance in the presence of high BP is the main subject of this review.

Today, cancer and cardiovascular disease (CVD) are the two principal causes of morbidity and mortality in humans. Both diseases are significantly related to age. In CVD, age is manifestly associated with alteration of the vascular endothelium and increased permeability to lipoproteins. There is an increase in senescent cells, which are characterized by loss of their replication capacity, which, of course, is little observed in cancer cells. Although the basic alterations of cancer cells remain largely unknown, cellular senescence is beginning to be widely used in cancer treatment and thus may help to better understand some mechanistic aspects of hypertension in humans.
The purpose of the present review is, within the cardiovascular (CV) system of hypertensive subjects: (i) to define the respective contribution of macrovessels and microvessels as well as their interaction; and (ii) to evaluate their specific role in CV risk. Regarding this second point, new aspects of cancer and CV mortality will be taken into account.

BLOOD PRESSURE PROFILE ALONG THE LARGE AND SMALL VESSELS

At the end of ventricular ejection, aortic pressure falls much more slowly than in the left ventricle. This alteration is due to specific features of the large arteries, particularly the aorta, which are elastic, and act as a reservoir during systole, storing some of the ejected blood, which is then forced out into the peripheral vessels during diastole (Windkessel effect). Thus, the pulse pressure (PP) generated by ventricular contraction travels along the aorta as a wave (Figure 1, A). The velocity of this wave (ie, pulse wave velocity, PWV) is calculated from the delay between two waves located at two different sites, when the distance between measuring sites is known (Figure 2). Simultaneous BP measurements at different points along the aorta show that the pressure wave changes shape as it travels down the aorta. Whereas systolic blood pressure (SBP) actually increases with distance from the heart, the mean level of the arterial pressure (MAP), together with diastolic blood pressure (DBP), falls slightly (by about 4 mm Hg) during the same course along the length of the aorta (Figure 1, A). Thus the amplitude of pressure oscillation between systole and diastole, ie, PP, nearly doubles (Figure 1). This process of PP amplification continues in the branches of the aorta as far as about the third level of branches. Thereafter, both PP and MAP decrease rapidly to the levels found in the microcirculation, where a quasi steady flow is achieved. Thus: (i) the macrocirculation is characterized by pulsatile flow as well as by the propagation of the pressure wave, together with PWV changes and PP amplification; and (ii) the microcirculation is influenced by steady flow, and hence by Poiseuille’s law, which states that the pressure gradient is proportional to the velocity and viscosity of blood, to the length of the arteriolar tree, and is inversely proportional to the vascular diameter to the power of four.

Several animal studies have examined the hydrostatic pressure profile along the macrocirculation and

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**Figure 1. Pressure wave along the arterial tree.**

A. The forward pressure wave is propagated from the heart toward the microvascular network at a given PWV; pulse pressure is higher in peripheral than in central arteries, due to a higher SBP and a slightly lower DBP; B. the pressure wave is reflected and the principal reflection sites are located in the microvascular network; C. the backward pressure wave returns toward the heart at the same PWV as the pressure wave. The arterial BP curve is in fact the summation of the incident and reflected pressure waves at each point of the arterial (aortic) tree.1,2,5

**Abbreviations:** BP, blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.
the microcirculation, ie, between the heart and capillaries. The general consensus is that BP reduction occurs predominantly in pre-capillary vessels ranging from 10 to 300 µm. Conversely, very high vascular resistance (which represents the mechanical forces that are opposed to blood flow) builds up abruptly from larger to smaller arteries, over a short transitional length of the path between arteries and veins, thus causing a dramatic decrease in MAP. At the same time, PP amplitude decreases, resulting in an almost completely steady flow through resistance vessels. Finally, a further contribution to opposition to flow derives from the reflection of arterial pulsations that cannot enter the high resistance vessels and are summated with pressure waves approaching the area of high resistance. This area of reflection, which is directly related to the number and geometrical properties of arteriolar bifurcations, will be analyzed in detail at the end of this review.

**HISTOMORPHOMETRIC CHARACTERISTICS OF THE ARTERIAL AND ARTERIOULAR WALL**

The architecture of arterial and arteriolar vessels is commonly described in terms of cross-sectional arrangement of vascular smooth muscle (VSM) cells and extracellular matrix (ECM). The former predominates in arterioles (microcirculation) and the latter in large arteries (macrocirculation). Large arteries are constituted, within the media, of lamellae of elastic material with intervening layers of VSM cells, collagen fibers, and ground substance. In the proximal aorta, elastin is the dominant component, while in the distal aorta the collagen-to-elastin ratio is reversed and, in peripheral arteries, collagen predominates. This is in accordance with the genetic expression and chemical properties of elastin, collagen, and VSM cells along the aorta and its branches. The protein product of the elastin gene is synthesized by VSM cells and secreted as a monomer, tropoelastin. After posttranslational modification, tropoelastin is cross-linked and organized into elastin polymers that form concentric rings of elastic fenestrated lamellae around the arterial lumen. Elastin-deficient mice die from an occlusive fibrocellular condition caused by subendothelial proliferation and accumulation of VSM cells in early neonatal life. Vascular collagen, for its part, is determined at a very young developmental stage and remains quite stable thereafter, due to a very low turnover. The proportion of type I and III collagen has a direct mechanical impact on vessel wall stiffness. Neurohumoral factors, particularly those related to angiotensin II and aldosterone, modulate collagen accumulation. Collagen is also subjected to important chemical modifications, such as breakdown, cross-linking, or glycation, resulting in marked changes in stiffness along the vessel wall.

ECM is responsible for the passive mechanical properties of the arteries, in particular of the aorta and its main branches. In a cylindrical vessel, when transmural pressure rises, a curvilinear pressure-diameter curve ensues, mainly due to the recruitment of elastin at low pressure and of collagen fibers at high pressure. Several other molecules, through their role in cell-cell and cell-matrix attachments, may contribute to the three-dimensional distribution of mechanical forces within the arterial wall. In rat proximal elastic arteries, the main VSM cell type consists of desmin-negative cells with high levels of connexins Cx43. In small- to medium-sized muscular arteries, the main VSM cell type is desmin-positive, with low levels of Cx43. In mice lacking desmin, isobaric carotid stiffness is increased

VSM cells do not represent a homogenous population. They consist of various proportions of phenotypes, with differences not only in contractile and secretory properties, but also in proliferative and apoptotic behavior. The distribution of these phenotypes is mainly influenced by age, location within the vascular tree, and presence of underlying pathological factors. Contractile properties, which are mainly expressed in arterioles, are responsible for the active mechanical properties of small and large vessels. Changes in VSM tone may occur either directly or through signals arising from endothelial cells. Endothelium is a source of various substances, particularly nitric oxide (NO), and of signal transduction mechanisms, which influence the biophysical properties of vessels.

Many of these signals are influenced by blood flow, through endothelium-dependent dilatation, which is not restricted to vessels of a particular size (muscular or musculoelastic). In contrast, the role of mediators of endothelial origin predominates in muscular distal arteries. The wall:lumen ratio of such vessels is influenced by the local differential effects of NO and other vasodilator (bradikinin–prostaglandins) or vasoconstrictor (norepinephrine, angiotensin, endothelin) agents. Whether such arteriole changes may modify the pattern of wave reflections issued from distal VSM cells is yet the subject of emerging research, particularly from a genetic standpoint.
PATHOPHYSIOLOGY OF RESISTANCE VESSELS AND MICROCIRCULATION IN HYPERTENSION

The function of the microcirculation is to optimize nutrient and oxygen supply within the tissues in response to variations of demand, and to minimize large fluctuations of hydrostatic pressure in the capillaries causing disturbances in capillary exchange. In hypertension, the main question is to determine under which conditions a large drop in hydrostatic pressure may be achieved from the larger to the smaller arteries without any deleterious effect on capillary pressure causing organ damage.

The most obvious mechanism increasing resistance to flow in arterioles is vasoconstriction. Only small changes in lumen size are required to make large adjustments in flow and pressure. Vasomotor tone in resistance arteries is controlled by local or metabolic regulation and by the sympathetic nervous system. In addition, paracrine substances, mostly released by the endothelial cells, play a key role in the control of local vasomotor tone. Endothelin and prostaglandin H2/thromboxane A2 are the most important vasoactive candidates to consider in the mechanisms of hypertension.

The tone of the microcirculation and, consequently, the levels of tissue perfusion are tightly coupled to the status of tissue-oxygen consumption. When oxygen requirements are increased, blood inflow increases accordingly. The ability of a vascular bed to constrict and dilate in order to maintain flow during changes in perfusion pressure, independently of any systemic neurohumoral regulation, is termed “autoregulation.” In the coronary circulation, autoregulation is most effective between pressures of 40 and 160 mm Hg. Importantly, chronic hypertension shifts the range of pressures over which autoregulation occurs in the myocardium, so that flow will begin to decline at greater pressure. A similar hemodynamic mechanism has been observed within the renal and the cerebral circulation.

Hypertrophy of the vascular wall, resulting in decreased lumen size, and medial hypertrophy, resulting in heightened vasodilated vascular resistance, are concepts that have received considerable attention in models of secondary hypertension. Independently of changes in the wall lumen ratio, Hutchins et al. first described up to 50% rarefaction of the microvasculature in the cremaster muscles of the spontaneously hypertensive rat (SHR), and Prewitt et al. subsequently found rarefaction of capillaries and arterioles in SHR gracilis muscle. There is now much evidence that the development of hypertension is accompanied by a diminished density of arterioles and capillaries in both animal and human models. Rarefaction can be either functional, resulting from vasoconstriction strong enough to close the vascular lumen and prevent the perfusion of a capillary bed, or structural, in which case the vessels are absent or their density is decreased in perfused tissues. Mainly arteriolar and capillary structural rarefaction may greatly contribute to the basic mechanisms of hypertension. It is possible that this process may result from the net effect of combined growth and apoptosis and may even vary in the presence of local associated cancer. Furthermore, the rarefaction process may predominate in specialized organs or tissues, such as the kidney. Numerous experimental studies and significant statistical associations between reduced nephron numbers and high BP strongly suggest this latter possibility.

CHANGES IN SBP AND PP AND CROSSTALK BETWEEN MACRO- CIRCULATION AND MICROCIRCULATION

Studies in hypertension have consistently shown links between cardiac function and resistance vessels, as well as the role of small and large vessels in end-organ damage. These links are traditionally described as exclusively due to specific neurohumoral or cellular mechanisms. However, sophisticated mechanical factors, particularly wave reflections, may also participate in this process.

Ejection of blood into the aorta generates a BP wave that is propagated to other arteries throughout the body. As in elastic conduits, this forward-traveling pressure wave is reflected at all points of structural and/or functional discontinuity of the arterial tree, ie, mainly at the origin of resistance arteries. A reflected wave is thus generated, which travels backward toward the ascending aorta. Incident and reflected pressure waves are in constant interaction along the arterial circuit and are summed up into the actual pressure wave. The final amplitude and shape of the measured aortic BP wave are determined by the phase relationship (timing) between the two components of these waves. In younger subjects, under physiological conditions with elastic arteries, the backward pressure wave returns from the distal arterioles during diastole, making PP higher in peripheral than in central arteries and boosting coronary perfusion. In older sub-
jects with stiff arteries and hence heightened PWV, the reflecting sites corresponding to arteriolar branching appear “closer” to the ascending aorta and the reflected waves occur earlier (Figure 3),34 being more closely in phase with incident waves in this region. Such an earlier return of wave reflections results in an augmentation of aortic and ventricular pressures during systole and reduces aortic pressure during diastole, favoring myocardial ischemia (Figure 3). Hence, altered mechanical properties of the aortic wall influence the level of aortic SBP (which is increased) and DBP (which is decreased). Finally, a disturbed pressure signal arising from arterioles modifies wave reflections, worsens the heart-vessel coupling, and favors CV complications. Evidence for this pathophysiological process has been highlighted by the role of PWV and wave reflections as independent CV risk factors in subjects with hypertension and other types of CVD15-38 and should be taken into account.

Importantly, wave reflections alter the ventricular-vascular coupling not only through increased arterial stiffness and change in timing, but also through modifications in their amplitude. This process depends on the reflectance properties of the vascular bed, which mainly arise from the microvascular network. Every change in the local properties of an artery may be the site of partial reflection of the pressure wave, in the same way that any discontinuity in a stretched string is a source of reflection. The geometry, number, structure, and function of smaller muscular arteries and arterioles, and ultimately microvascular rarefaction, influence these reflections. Taylor previously reported that an increase in the arterial cross-sectional area at peripheral bifurcations causes a delay in wave reflections with subsequent selective decreases in SBP and PP through changes in peripheral reflection pattern.39 In subjects with hypertension, an opposite pattern may be described, resulting from hypertrophy and/or remodeling of arteriolar vessels.5 Furthermore, age greatly influences all these modifications and tends to increase SBP and PP more rapidly in the central than in the distal arteries, causing a reduction in SBP and PP amplification. This reduction also constitutes an independent predictor of CV mortality in hypertensive subjects.40

**CONCLUSIONS AND PERSPECTIVES**

The present description has shown that, within the vascular tree, elastic arteries buffer the pulsations, muscular arteries actively alter propagation velocity, and arterioles serve not only as resistance vessels, but also as major reflection sites. Within the CV system, all these alterations (or their combination) enables continuous crosstalk between the heart and the microvascular network2-5 The disturbance of these frequency-dependent alterations favors a predominant increase in SBP and PP, as observed in aged and/or hypertensive populations at high CV risk. This whole process contributes to increasing the load of the heart and favoring cardiac hypertrophy and coronary ischemia, finally causing CV death.41 All these findings indicate that reduction in SBP and PP has a major impact on CV prevention. Recent studies on cancer have shown that antiangiogenic medications42-44 may poten-
tially increase BP and therefore may be used as comparators for the treatment of hypertension. However, to date, these drugs have been investigated mainly in terms of renal microcirculation and DBP, but not SBP and PP.45

Our findings suggest that CV prevention may contribute to decreasing risk not only through reduction in SBP and PP, but also through the decline in baseline CV risk factors, as has been shown in the past.46 In recent years, only two major studies have attempted to detect the principal risk factors liable to separately predict cancer and CVD in humans (Yusuf et al47 and Danaei et al48). Comparison of the two studies indicates that only four risk factors are reported to be common to CVD and cancer: smoking, increased body weight, physical inactivity, and reduced consumption of fruit and legumes. Other factors are observed, but less relevant, such as pollution and sociopsychological or educational factors. We suggest that CVD and cancer prevention should be studied together on the basis of these four risk factors.

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Lessons From the Oncologist

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2013;18:45-55

1. Tumor angiogenesis: therapeutic implications

2. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy
   D. Cardinale and others. Circulation. 2004

3. Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies

4. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition
   D. Cardinale and others. Circulation. 2006

5. Blood pressure rise following angiogenesis inhibition by bevacizumab: a crucial role for microcirculation

6. Cardiovascular toxicity caused by cancer treatment: strategies for early detection
   R. Altena and others. Lancet Oncol. 2009

7. Cardiac toxicity with anti-HER-2 therapies—what have we learned so far?
   E. de Azembuja and others. Target Oncol. 2009

8. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know
   M. S. Ewer and S. M. Ewer. Nat Rev Cardiol. 2010

9. Cardiac disease and heart failure in cancer patients: is our training adequate to provide optimal care?
   C. L. Chen and R. Steingart. Heart Fail Clin. 2011

10. Effects of novel angiogenesis inhibitors for the treatment of cancer on the cardiovascular system: focus on hypertension
    B. Nazer and others. Circulation. 2011

Selection of seminal papers by Bernard Lévy, MD, PhD
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J udah Folkman (1933-2008) was a cardiac surgeon originally involved in the usual problems of cardiac surgeons: from 1956 to 1971, he worked on anesthesia and analgesia, he studied new methods for measuring blood gas pressure, techniques for portacaval shunts, etc. In 1968, he became the youngest full Professor at Harvard Medical School in history. His fascination with the vascular circulation can be traced to his boyhood in Bexley, Ohio, USA, during which he could be found most often in his basement laboratory working on his own scientific projects.

One such project involved participating in a scientific competition with the goal of keeping a perfused rat heart beating for as long as possible outside of the body. According to the story, Folkman's complex homemade perfusion apparatus and special perfusion formula kept the heart beating well beyond that of all the other entrants. Interestingly, tissue perfusion, vascularization, and tissue growth and survival were crucial elements in Folkman’s career in science and medicine.

In 1971, Folkman published his first paper in relation with angiogenesis in *N Engl J Med*. He postulated that all cancer tumors are angiogenesis-dependent. Folkman’s initial theory was very simple: if a tumor could be stopped from growing its own blood supply, it would wither and die. Folkman proposed that “new capillary growth is elicited by a diffusible factor generated by malignant tumor cells. In the absence of neovascularization most tumors might become dormant at a tiny diameter, perhaps 2-3 mm.” Though this hypothesis was initially disregarded by most experts in the field, Folkman persisted with his research. After more than a decade, his theory became widely accepted and is now being exploited in the treatment of a growing number of diseases, including blindness caused by macular degeneration. Actually, vascular endothelial growth factor (VEGF) was discovered 18 years later. VEGF binding to the receptor VEGFR-2 causes receptor dimerization and autophosphorylation at several tyrosine kinase residues. VEGFR-2 autophosphorylation also causes activation of the phosphoinositide-3-kinase–Akt pathway, which then further phosphorylates and activates endothelial nitric oxide synthase (eNOS), leading to vasodilatation and angiogenesis. The first antiangiogenic agent, a humanized VEGF antibody, was approved by the US Food and Drug Administration in 2004. Folkman’s research has led to the development of progressively more potent compounds, such as angiotatin, endostatin, vascularostatin, caplostatin, and lodamin, that have successfully halted the growth of tumors in laboratory mice. Two angiogenesis inhibitors based on Folkman’s hypothesis and developed by Genetech, Lucentis and Avastin, are now FDA-approved for use in age-related macular degeneration and some metastatic cancers respectively. The 1971 *N Engl J Med* paper not only elaborated Folkman’s full-blown theory of tumor angiogenesis, it also provided the underpinnings for nearly four decades of his future research and the frame for a field of discovery that barely existed at the time. NO depletion may be a common factor contributing to the pathogenesis of side effects associated with VEGF-blocking agents. It remains unproven, however, whether replacing NO to treat the adverse events related to VEGF inhibition or using NO donors to prevent the toxicity may have negative impact on the effectiveness of these novel and very effective therapeutic agents.

Folkman’s career and life story is a rare example of true translational research: from highly speculative and still nonvalidated pathophysiological hypothesis toward major changes in concepts and new therapeutics.

Gerhard Herzberg is awarded the Nobel Prize in Chemistry for his work on the electronic structure of molecules and free radicals; Première of “Play Misty for Me,” Clint Eastwood’s directorial debut; and Shenouda III of Alexandria is enthroned the 117th Pope and Patriarch of the Church of Alexandria.
**Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy**


*Circulation*. 2004;109:2749-2754

Cardiotoxicity is important as a limiting factor in the use of a wide variety of drugs whose therapeutic indications for life-threatening diseases merit serious side-effect profiles, such as anticancer and antiretroviral drugs. For such drugs, it is especially important to have reliable safety biomarkers to monitor and direct therapeutic strategy.

There are two broad categories of adverse effects to be considered, functional and structural effects. Seriously altered function may be completely dissociated from structural effect, especially at an early stage. For example, electrophysiological effects of drugs are typically mediated by their direct interaction with cardiac ion channels, which may lead to prolongation of the QT interval or arrhythmia that predisposes the patient to a myocardial event such as torsades de pointes. In the same way, myocardial injury related to drug toxicity could result in left ventricular function alteration objectivized by a decrease in its ejection fraction. However, since decreased left ventricular ejection fraction ensues only after full compensation is no longer achieved, maintained left ventricle function as measured by cardiac ultrasound or nuclear techniques should be considered neither as an indicator of normal myocardium nor as an evidence of absence of cardiotoxicity.

Troponin I is a protein present exclusively in the myocardial cells. Troponin I plasma concentration is a well-established specific and sensitive marker of myocardial injury, with both high diagnostic and prognostic value. Since 2000, cardiac troponin has been declared as the better biomarker for myocardial infarct by the American College of Cardiology and the European Society of Cardiology. This reflects its high sensitivity and nearly absolute specificity. As well as being the gold standard for cardiac injury in cardiology, it has been widely used for clinical assessment and monitoring of cardiac toxicity in patients treated for cancer. Low cost, wide availability, and extensive validation in other forms of heart disease make troponin attractive as a potentially sensitive tool for the detection of early chemotherapy damage. In 703 cancer patients (breast cancer (n=326), high-grade non-Hodgkin's lymphoma (n=264), myeloma (n=44), Hodgkin's disease (n=30), ovarian carcinoma (n=16), small-cell lung cancer (n=10), others (n=13)), Cardinale and colleagues showed that troponin is a sensitive and specific marker for myocardial injury in patients treated with anticancer drugs and is able to predict, at a very early phase, both the development of future left ventricular dysfunction and its severity. Stratification of patients according to the plasma level of troponin I allowed them to differentiate the monitoring program and to plan, in selected patients, preventive strategies aimed at improving clinical outcome.

However, according to recent guidelines, the predictive role for biomarkers of cardiotoxicity caused by cancer treatment is not defined well enough to include them as routine screening measurements, although persistent increases in cardiac troponin or N-terminal pro-B-type natriuretic peptide concentrations seem to identify patients at risk for cardiotoxicity. Therefore, these biomarkers might aid in early detection of subclinical damage. A useful approach is to assess baseline biomarker concentrations in every patient and measure periodically during and after a potentially cardiotoxic cancer treatment. Increases in concentrations of these markers might signal the need for further cardiac assessment.

Norway follows Ireland's lead to become the second nation to ban smoking in all bars and restaurants; Former US President Ronald Reagan dies at the age of 93 from complications arising from Alzheimer's disease; and the gun used by Gavrilo Princip to assassinate Archduke Franz Ferdinand of Austria, triggering the First World War, is found in a Jesuit monastery in Austria.
Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies

K. A. Wouters, L. C. Kremer, T. L. Miller, E. H. Herman, S. E. Lipshultz

Br J Haematol. 2005;131:561-578

Over the last 40 years, great progress has been made in treating childhood and adult cancers. The discovery of doxorubicin, an anthracycline antitumor antibiotic, in the early 1960s was a major advance in the fight against cancer. As a result of the introduction of anthracyclines, together with other improvements of treatment, cancer survival has improved markedly, particularly among children, where survival rates have increased from 30% in the 1960s to 70% currently. However, this progress has come at an unforeseen cost, in the form of emerging long-term effects of anthracycline treatment. A major complication of anthracycline therapy is its adverse cardiovascular effects. The use of anthracyclines is limited by dose-dependent cardiotoxicity, which may be the dose-limiting factor in cancer treatment. Furthermore, cardiotoxicity can lead to long-term side effects and severe morbidity. Several preventive measures are currently being used, including limiting cumulative dose, altering anthracycline administration, using anthracycline analogs, adding cardioprotectants to the regimen and employing nutritional supplements.

Limiting the cumulative dose of anthracyclines is the most obvious way to limit their cardiotoxicity; however, there is no absolute safe dose of anthracycline below which cardiotoxicity does not occur. Especially for late-onset chronic progressive cardiac dysfunction, we do not know what the lifetime safe dose of any form of anthracycline is.

Replacing bolus administration of anthracycline with slow infusion remains controversial. Continuous infusion reduces peak anthracycline levels, but prolongs exposure and may inhibit recovery of the cardiomyocytes damaged by anthracyclines. However, it seems that continuous infusions over 48 or 96 h are less cardiotoxic in adults, when cardiac effects are assessed during or shortly after therapy. Many analogs of anthracycline are used; their toxicity is roughly similar, but they can have more antitumor effect for lower administered doses and thus lower cardiotoxicity. Liposomal anthracyclines were developed to reduce the cardiotoxicity of doxorubicin while preserving its antitumor efficacy. Intravenously administered liposomes cannot escape the vascular space in sites that have tight capillary junctions, such as the heart, at least in theory. In tumor vessels with abnormal endothelium and high vascular permeability, liposomes cross the vessel wall barrier and attain the tumor itself. Most studies indicate that the activity of liposomal doxorubicin, and especially of pegylated liposomal doxorubicin, is similar to that of conventional doxorubicin, whether given alone or in combination; as expected, the risk of cardiotoxicity is markedly lower.

Addition of various “cardioprotectants” to anthracyclines has been tested: probucol, amifostine, N-acetylcysteine, without clear evidence-based clinical results. Carvedilol and sildenafil have also been proposed, but no randomized clinical trials were found that studied their cardioprotective properties in humans.

Dexrazoxane is thought to be the only cardioprotective agent with proven efficacy in cancer patients receiving anthracycline chemotherapy. Dexrazoxane’s activity against doxorubicin-induced cardiotoxicity may be attributable to the intracellular conversion to an open-ring derivative (ADR-929) that chelates iron. Clinical trials have found that dexrazoxane is a highly effective cardioprotectant. However, it has been suggested that dexrazoxane might interfere with the antitumor activity of doxorubicin. An extensive review of available data and results allows to conclude that prevention and early treatment of anticancer drug-induced cardiotoxicity is certainly underexplored and thus underutilized. Avenues for prevention and early treatment of cardiotoxicity are available and must be better explored.

2005

U2 singer Bono, Melinda Gates, and Bill Gates are named Time’s Persons of the Year; São Paulo defeats Liverpool FC 1-0 to win the FIFA Club World Championship in Yokohama, Japan; and the video-sharing Web site YouTube is founded.
Although anthracyclines are highly effective in treating certain cancers, their use is limited by their potential for cardiotoxicity. Studies report a wide range in the incidence of cardiotoxicity, related to differences in definitions, chemotherapy regimens, and patient populations. The incidence of clinical heart failure is 1% to 5%, and that of asymptomatic decrease in left ventricular function is 5% to 20%. Thus, identification of individuals at risk, prevention, early diagnosis, and effective treatment are all important goals. Most of these needs have been addressed by uncontrolled or small studies, and guidelines have relatively sparse information on which to base recommendations for care, other than careful monitoring of left ventricular function and interrupting or discontinuing anthracyclines once significant decrease in ejection fraction is detected, which is often too late. A number of other agents including erythropoietin, thrombopoietin, and iloprost have shown promise in animal models, although it is not clear how well these models predict human response.

Cardinale and colleagues reported, for the first time, a randomized trial of patients after high-dose chemotherapy. The authors addressed two major challenges: How does one identify who is likely to develop (or is developing) cardiotoxicity before left ventricular function decreases, and once an at-risk patient has been identified, how can one prevent deterioration in left ventricular function? One hundred fourteen adult patients who had elevated troponin I soon after high-dose chemotherapy (one-quarter of the treated population) were randomized to enalapril (target of 20 mg/day) or open-label control, with treatment initiation delayed until 1 month after chemotherapy and continued for 1 year. The results were spectacular: 43% of controls had a more than 10% drop in left ventricular ejection fraction, none in the enalapril group. Clinical cardiac events were likewise nearly eliminated with enalapril, from 30 events in the control population to 1 event with enalapril. This was primarily attributable to reduction in heart failure and arrhythmias. As the trial was single-center, open-label, some bias (especially in the subjective clinical end points) could be expected.

Experience in heart failure trials has taught us to be skeptical of very large and unexpected treatment effects, particularly in small trials. Is it plausible that treatment of subclinical cardiac toxicity with an angiotensin-converting enzyme inhibitor would completely eliminate deterioration of ejection fraction and clinical events? Angiotensin-converting enzyme (ACE) inhibitors have been shown to be remarkably effective across a broad range of cardiovascular conditions, and they generally result in an approximately 20% relative risk reduction in clinical events. Moreover, another similarly sized randomized trial studying an anthracycline-treated pediatric population with cardiac abnormalities at the time of enrollment showed only modest benefits of enalapril in improving cardiac function. Thus, even if the treatment effect seen in this small trial were an overestimate, the concept that ACE inhibitors may prevent heart failure in at-risk populations is not a novel one. Furthermore, the risk added by ACE inhibitors is very low and it would be reasonable to recommend their use for prevention of chemotherapy-induced cardiotoxicity on the basis of this study. Because cardiomyopathy may appear late, would treatment with ACE inhibitors for longer than 1 year prevent later development of heart failure? This is an important unanswered question.

Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition


Circulation. 2006;114:2474-2481

Former US president Gerald Ford dies, aged 93; the United Kingdom repays the last of its debts to the United States and Canada from World War II; and former president of Iraq Saddam Hussein is executed.
Arterial hypertension is the most commonly reported side effect in every clinical trial testing inhibitors of angiogenesis and especially inhibitors of vascular endothelial growth factor (VEGF)/VEGFR-2 signaling. Whatever their initial level of blood pressure, patients receiving antiangiogenic treatment show rapid and significant increases in both systolic and diastolic arterial pressure; however, in a majority of patients, blood pressure values do not reach the levels characterizing clinical hypertension. The mechanism of hypertension following pharmacological blockade of angiogenesis remains mysterious. Measurement of circulating concentrations of VEGF, total catecholamines, epinephrine, norepinephrine, endothelin I, urotensin II, renin, and aldosterone were performed and activation of the sympathetic system was, until recently, the generally acknowledged cause of antiangiogenic-induced hypertension. Unlike tumor vessels that have VEGF as survival factor, the normal adult vasculature was widely regarded as largely independent of VEGF for survival, stability, and normal function. Indeed, the rationale for using VEGF inhibitors on tumors was based on the assumption that tumor vessels can be impacted without harming other vessels.

Actually, studies of the effects of VEGF antibody in experimental models indicated that VEGF participates in blood vessel survival and plasticity in adult life and not only during the developmental period. Examination of the simple vascular network of the mouse trachea revealed regression of some normal mucosal capillaries following treatment with VEGF antibody. Effects of VEGF antibody on the capillary networks were observed as early as 6 hours after drug injection in mice. After inhibition of VEGF signaling for 1-3 weeks, significant capillary regression occurred in pancreatic islets, thyroid, adrenal cortex, pituitary, small intestine villi, choroid plexus, adipose tissue, and trachea.

The amount of regression was dose dependent and varied from organ to organ, with a maximum of 68% in thyroid. The experimental link and crossed relationships between VEGF and the nitric oxide (NO) pathway are clearly established. Endothelial dysfunction and capillary rarefaction are hallmarks of common arterial hypertension. Thus, the authors postulated that NO would play a crucial role in the vascular response to angiogenesis inhibitors.

VEGF both enhances endothelial nitric oxide synthase (eNOS) activity and upregulates the message and protein levels of the VEGF receptor in human endothelial cells. NO generation is therefore an essential component of the response pattern to angiogenic growth factors; thus VEGF blockade and NO inhibition could result in several common abnormalities. “Endothelial dysfunction” and “microvascular rarefaction” can be observed in most situations with increased cardiovascular risk. As expected, the authors evidenced major endothelial dysfunction in patients receiving the VEGF antibody bevacizumab. Furthermore, these patients evidenced significant dermal capillary rarefaction after bevacizumab treatment. This clinical paper was the first to propose pathophysiological mechanisms explaining antiangiogenic-induced hypertension. Furthermore, the beneficial effect of antiangiogenic treatment on the tumor vasculature could be related to its efficiency on the healthy vessels. Thus, the authors raised the hypothesis that arterial hypertension could be an early marker of antitumor efficiency of angiogenesis blockade. This hypothesis has been confirmed in several large clinical trials, though not in others; probably depending on the type and localization of cancer.

Dmitry Medvedev is elected the third President of Russia; a major earthquake in the Sichuan province of China leaves an estimated 68 000 people dead; and veteran Portuguese film director Manoel de Oliveira is awarded a Palme d’Or for his lifetime career achievement at the 2008 Cannes Film Festival.
Cardiovascular toxicity caused by cancer treatment: strategies for early detection

R. Altena, P. J. Perik, D. J. van Veldhuisen, E. G. de Vries, J. A. Gietema


Cardiovascular toxicity is one of the most devastating complications of cancer treatment and can arise during or shortly after treatment, or even several years later. In trials of adjuvant anthracycline-based treatment for breast cancer, 5-year incidence of chronic heart failure is between 0% and 3.2%, depending on the combination regimen and cumulative dose of anthracycline. And yet long-term follow up of cardiovascular morbidity and mortality is not available.

A large meta-analysis of the Early Breast Cancer Trialists’ Collaborative Group, in which 42,000 patients with breast cancer participated in 78 randomized trials, found that patients treated with radiotherapy had a high rate of non-breast cancer mortality, mainly from heart disease (rate ratio 1 to 12). This high rate of heart disease was observed during the first 5 years after treatment and continued for up to 15 years. Determination of the left ventricular ejection fraction (LVEF) is the most common method to screen for toxic effects on the heart, however, this approach underestimates cardiac damage, due to the extraordinary capacity of the heart to adapt itself to deleterious conditions, so that measurement of LVEF alone delays diagnosis. Additional strategies to monitor treatment-induced cardiotoxicity are being explored. Guidelines for monitoring have been formulated for several cancer treatments; however, appropriate underlying evidence is still largely absent. In this review, the authors summarized conventional and contemporary methods for early detection of cardiotoxicity and defined a level of evidence for the basis of each method. Little evidence is available to define a role for ECG in the assessment of potential cardiotoxicity. Several individual cohort studies suggest that a prolonged corrected QT interval is an early marker of cardiotoxicity, but the accuracy for prediction of late cardiac disease is not established. Despite its limitations, echocardiography is mainly used to assess changes in LVEF during cancer treatment. Several reports indicate that newer diastolic measures such as tissue velocity imaging of the early diastole, strain, and strain rate enable early detection of subclinical changes in cardiac function during cancer treatment, although their predictive value remains unclear. With high reproducibility and low interobserver and intraindividual variability, multigated scintigraphy (MUGA) could be the gold standard for assessing LVEF. However, MUGA is somewhat insensitive in detecting subtle changes in cardiac function, and thus has limited value for early detection of cardiotoxicity.

Plasma dosage of troponins and atrial natriuretic peptides are the better-explored biomarkers of cardiotoxicity. The most useful approach is to assess baseline biomarker concentrations in every patient and make measurements periodically during and after a potentially cardiotoxic cancer treatment. Increases in concentrations of these markers may signal the need for further cardiac assessment. Markers of endothelial damage, targeted cardiac imaging, and MRI are likely interesting techniques; however, they are still in the realm of research.

Current guidelines and monitoring strategies for detection of cardiovascular toxicity caused by cancer treatment are mostly derived from medium-level evidence. Thus, it is clear that despite the major problems of cardiotoxicity in oncology, there is no clear and recognized parameter for the early detection of cardiovascular damage. Plasma troponin and atrial natriuretic peptide could be valuable surrogates. A major point must be underlined: when LVEF declines, heart function has already been altered for a long time and it could already be too late.

The genome of a female Hereford cow is fully sequenced by researchers at the National Institutes of Health and the US Department of Agriculture; 8 people are killed and 17 injured when a car is driven at high speed into a crowd attending a Queens Day parade in Apeldoorn, Netherlands; and Argentine golfer Ángel Cabrera wins the 2009 Masters Tournament.
Targeted therapy is a recent concept developed by oncologists; basically, a targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth, rather than by "simply" interfering with rapidly dividing cells (e.g., with traditional chemotherapy). Targeted cancer therapies are hoped to be more effective than current treatments and less harmful to normal cells. The concept of "targeted" therapies implies that such drugs only act on cells that specifically express the particular target, therefore giving rise to a low incidence of side effects. Definitive experiments showed, in 1986, that targeted therapy would reverse the malignant phenotype of tumor cells involved treating Her2/neu transformed cells with monoclonal antibodies in vitro and in vivo.

Breast cancer is the most common malignant tumor affecting women. The HER receptors are proteins that are embedded in the cell membrane and communicate molecular signals from outside the cell to inside the cell, and switch genes on and off. The HER proteins regulate cell growth, survival, adhesion, migration, and differentiation—functions that are amplified or weakened in cancer cells. In some cancers, notably some breast cancers, HER2 is overexpressed, and causes breast cells to reproduce uncontrollably. Trastuzumab is an antibody that binds selectively to the HER2 protein. When it binds to defective HER2 proteins, the HER2 protein no longer causes cells in the breast to reproduce uncontrollably. This increases the survival of people with cancer. However, cancers usually develop resistance to trastuzumab. The original studies of trastuzumab showed that it improved overall survival in late-stage (metastatic) breast cancer from 20.3 to 25.1 months.

Trastuzumab and lapatinib, a dual tyrosine kinase inhibitor of EGFR and HER-2, are approved for the treatment of metastatic breast cancer patients after failure of prior treatment with anthracyclines, taxanes, and trastuzumab in combination with capecitabine. These targeted therapies currently approved for the treatment of breast cancer have been associated with a relatively high incidence of cardiovascular events. The anti-HER2 agents trastuzumab and lapatinib may cause left ventricular dysfunction or even congestive heart failure. Importantly, cardiac toxicity, manifested as symptomatic congestive heart failure or asymptomatic left ventricular ejection fraction decline, has been reported in some of the patients receiving these novel anti-HER-2 therapies, particularly when these drugs are used following anthracyclines, whose cardiotoxic potential has been recognized for decades. Several anti–human epidermal growth factor receptor 2 (HER2) and antiangiogenic agents plus their combinations are currently being developed and evaluated for the treatment of breast cancer. This important review focuses on the incidence, natural history, underlying mechanisms, management, and areas of uncertainty regarding trastuzumab- and lapatinib-induced cardiotoxicity.

Once again, cardiology and oncology markedly differ: in cancer, the time scale of survival is given in months and, after a few years, the percentage of surviving patients is much smaller than that of patients after myocardial infarction, for example, 20 years after diagnosis. This review aims to assess the incidence of cardiac adverse events associated with targeted therapies designed to block HER2 and angiogenic pathways.

Cardiac toxicity with anti-HER-2 therapies—what have we learned so far?

E. de Azemiju, P. L. Bedard, T. Suter, M. Piccart-Gebhart

Target Oncol. 2009;4:77-88

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2009

ETA military leader Jurdan Martitegi is arrested in Monaural, southern France;
Oracle Corporation acquires Sun Microsystems for $7.4 billion; and a swine flu outbreak in Mexico kills at least 149 people
Cardiotoxicity of anticancer treatments: what the cardiologist needs to know

M. S. Ewer, S. M. Ewer

*Nat Rev Cardiol.* 2010;7:564-575

Michael S. Ewer is an oncologist working at the Cancer Center, Anderson Hospital and Tumor Institute, Houston, Texas; Steven M. Ewer is a cardiologist at the University of Wisconsin School of Medicine and Public Health. Dr Steven Ewer offers specialty care for cancer patients with cardiovascular comorbidities or who develop cardiac complications from cancer or its treatment. In this paper, the two authors tell cardiologists what they need to know to manage patients with both cancer and cardiovascular disease. Unlike many other cell types, cardiac myocytes are not capable of extensive cellular replacement, yet we still have the capacity to increase cardiac output through exercise, or the ability to survive the loss of a large number of myocytes caused by a variety of insults.

The heart can be temporarily or permanently damaged by exposure to therapeutic agents, including those used for the treatment of cancer. The authors discuss the cardiac abnormalities that develop as a result of cancer treatment, with an emphasis on those that are most relevant to the consulting cardiologist involved in the management of this challenging group of patients. The prototypical example of cardiotoxicity due to anticancer treatment is anthracycline-related cardiomyopathy. Early observations demonstrated that left ventricular systolic dysfunction was related to the cumulative anthracycline dose, damage was permanent at the cellular level, and could lead to refractory heart failure and cardiac death. Novel drugs, such as the monoclonal antibody trastuzumab, have been introduced that also cause cardiomyopathy, but with clinical features that are fundamentally different from anthracycline-related disease, mimicking the stunning or hibernation phenomenon seen with myocardial ischemia. Cardiotoxicity induced by chemotherapy and radiotherapy includes cardiomyopathy, ischemia, arrhythmias, hypertension, pericardial disease, and thromboembolic disease. These conditions increase morbidity, often interfere with cancer treatment regimens, and can negatively affect long-term outcomes.

The approach to cardiovascular disease in patients with cancer is often different from that in the general population, not only because of distinctive underlying mechanisms and clinical features of their heart disease, but also because of the potential ongoing need for additional cancer treatment as well as the altered duration of anticipated survival.

Cardiologists have to remember that the concept of “evidence-based medicine” is very different in oncology and in cardiology. We (cardiologists) are used to waiting for a huge number of patients with a well-defined pathology and treatment before publishing guidelines based upon several concordant trials, preferably performed under prospective and double-blind conditions. In oncology, the number of new “targeted therapies” is so great and their introduction into the clinical practice so rapid that medical authorities and societies are struggling to establish evidence-based recommendations. So in contrast to anthracyclines and trastuzumab, used in large populations long enough to reach almost stable recommendations, most of the recently introduced drugs still do not have a clinical and epidemiological basis as solid as expected by cardiologists. The merit of the authors is to collect available data and propose a comprehensive and relatively simple review for cardiologists. The authors’ conclusion is obvious, but major: “An interdisciplinary approach is needed to foster communication between healthcare providers and ensure optimal patient outcomes.” This recommendation is likely one of the most important points made in the present summaries.

The 2010 Ig Nobel Prize for medicine is awarded to Simon Rietveld of the University of Amsterdam for his work demonstrating that asthma symptoms can be alleviated with a roller coaster ride; the 2010 Commonwealth Games begin in Delhi, India; and English actor, comedian, and singer-songwriter Sir Norman Wisdom dies in an Isle of Man nursing home at the age of 95.
Cardiac disease and heart failure in cancer patients: is our training adequate to provide optimal care?

C. L. Chen, R. Steingart

*Heart Fail Clin.* 2011;7:357-362

Carol Chen and Richard Steingart are cardiologists working at the Memorial Sloan-Kettering Cancer Center, New York, one of the world’s leading centers developing programs devoted exclusively to the management of cardiovascular disease in cancer patients. Their daily practice concerns patients receiving chemotherapy and experiencing cardiovascular side effects. In this very practical, pragmatic, and didactic article, the authors expose the challenge of delivering cardiac care during cancer treatment. The care of patients with cancer who have cardiac disease is dispersed both sequentially and concurrently across multiple providers. Thus, an important goal of education is communication among the providers regarding changes in therapy, toxicity of therapy, and symptom assessment.

A major point to consider is the increasing population at risk: about 12 million people diagnosed with cancer were living in the United States in 2007. Because of advances in the early detection and treatment of cancer, approximately 66% of people diagnosed with cancer are expected to live at least 5 years after diagnosis. Another special population that continues to grow because of the success of cancer treatment is the group of pediatric cancer survivors. More than 80% of children and adolescents who are treated for cancer become long-term survivors. In 2003, there were approximately 270,000 survivors of pediatric cancer in the United States, or approximately 1 in 640 adults between the ages of 20 and 39. The quantitative importance of these populations deserves specific attention, medical awareness, and adapted health structures.

Several considerations can delay or mask the diagnosis of heart failure in these patients; namely, a supposed lower priority of cardiac vs cancer care and the similarity of symptoms of heart failure and of the expected adverse effects of cancer therapy, such as fatigue, dyspnea, and lower extremity edema. Diagnosis of occult cancer and initiation of treatment by an oncologist may also result in delay in diagnosis and treatment of coronary artery disease, which may be exacerbated by treatment-related hypertension, ischemia, or heart failure.

How can clinicians be exposed to these critical clinical decisions so that patients with cancer receive optimal cardiovascular care? Because all oncology and cardiology trainees must go through internal medicine residency and fellowship training, the authors propose that purposeful and thoughtful exposure be initiated in these curricula. Six main topics could be included in a core curriculum for house staff in internal medicine, cardiology, and oncology, and other providers entering the field (nurse practitioners, advanced practice nurses, and physician assistants):

(i) left ventricular dysfunction, (ii) myocardial ischemia, (iii) arrhythmia, (iv) treatment-related hypertension, (v) pretreatment cardiac risk assessment (both medical and surgical therapy); and (vi) cancer survivorship care.

Goals for oncologists and primary care providers would focus more on awareness and surveillance of cardiovascular disease, whereas goals for cardiovascular specialists would focus more on appropriate identification and early treatment of cardiac toxicity in cancer patients. Finally, the authors propose a pragmatic multilevel approach that includes:

(i) a short, targeted curriculum for house staff training programs in internal medicine, family medicine, pediatrics, cardiology, and oncology, (ii) increasing presence at national meetings of internists, oncologists, and cardiologists; and (iii) an Internet-based repository of core information.

Albert II, Prince of Monaco, weds South African Olympic swimmer Charlene Wittstock; former Welsh rugby player Richard Parks becomes the first person to climb the highest summits on each of the world’s continents, as well as reach both the North and South Poles in a single year; and Neptune completes its first recorded orbit of the Sun since its discovery in 1846.
Effects of novel angiogenesis inhibitors for the treatment of cancer on the cardiovascular system: focus on hypertension

B. Nazer, B. D. Humphreys, J. Moslehi

Circulation. 2011;124:1687-1691

The National Cancer Institute Common Toxicity Criteria (CTC) system has substantially evolved since its inception in 1983. The Common Terminology Criteria for Adverse Events (CTCAE) represents the first comprehensive, multimodality grading system for reporting the acute and late effects of cancer treatment. The CTC builds on the strengths of previous systems, represents a considerable effort among hundreds of participants, and relies on international collaboration and consensus of the oncology research community. Until 2009, the National Cancer Institute defined 5 grades of severity of adverse effects as common toxicity criteria in relation with arterial hypertension:

• Grade 1: transient increase (<24 h) greater than 20 mm Hg (diastolic) or greater than 150/100 mm Hg.
• Grade 2: recurrent or persistent (>24 h) increase greater than 20 mm Hg (diastolic) or greater than 150/100 mm Hg.
• Grade 3: hypertension requiring therapy or more intensive therapy than previously.
• Grade 4: hypertensive crisis.
• Grade 5: death.

Criteria allowing assessment of toxicity associated with novel chemotherapies have been updated to more closely reflect the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines for hypertension very recently, in 2009. The recent evolution of these criteria underscores the need for more concerted action between cardiologists and oncologists.

In this article, Nazer and colleagues review the pathophysiological mechanisms responsible for hypertension in patients receiving antiangiogenic agents. Bevacizumab, a monoclonal antibody targeted against soluble vascular endothelial growth factor (VEGF) protein, was approved by the US Food and Drug Administration in 2004 for the treatment of metastatic colorectal cancer. Since then, small receptor tyrosine kinase inhibitors, with potent VEGFR-2 inhibition, have been approved for an array of malignancies. Activation of VEGFR-2 by VEGF induces expression of nitric oxide (NO) synthase in endothelial cells, which promotes vascular permeability and vasodilation. Treatment with angiogenesis inhibitors has been shown to decrease NO synthesis and lead to hypertension associated with suppression of the NO pathway. Other mechanisms likely play a role. Loss of parallel capillary circulation in normal, non-tumor tissue, (microvascular rarefaction), has also been associated with endothelial dysfunction in hypertensive patients treated with antiangiogenic drugs.

Initial clinical trials with bevacizumab first identified hypertension in 28% of the patients; subsequent trials with sorafenib, sunitinib, and pazopanib identified hypertension with similar frequency in all inhibitors of angiogenesis. Meta-analyses have shown the incidence of hypertension to be 19% to 24% with all antiangiogenic treatments. However, while oncologists are not fully aware of the importance of measuring arterial blood pressure in their patients, these data may underestimate the true incidence of hypertension in clinical practice today. Interestingly, the rise in blood pressure associated with VEGF inhibitors appears to reverse as rapidly as its onset, with a return of blood pressure to nearly baseline levels by the end of the off-treatment phase, an observation that has implications for patient management. Furthermore, patients in the general population may have more comorbidities, such as diabetes mellitus or preexisting hypertension, compared with highly selected trial patients. Therefore, nontrial patients may be at increased risk of developing angiogenesis inhibitor–induced hypertension. The management of these hypertensive patients is still not well defined and JNC 7 guidelines should be followed.

German horse Danedream wins the Prix de l’Arc de Triomphe in a course record time;
Helle Thorning-Schmidt becomes the first female Prime Minister of Denmark; and
Paul McCartney marries American heiress Nancy Shevell in London
# Lessons From the Oncologist

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selected by **Bernard I. Lévy, MD, PhD**

*Paris Cardiovascular Center INSERM U970 - Blood & Vessels Institute - 8 rue Guy Patin - 75010 Paris - France*

(e-mail: bernard.levy@inserm.fr)

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